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Alzheimer's disease: How metal ions define β-amyloid function

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Abstract

Alzheimer's disease is increasingly recognized to be linked to the function and status of metal ions, and recently, the amyloid hypothesis has been strongly intertwined with the metal ion hypothesis; in fact, these two hypotheses fit well together and are not mutually contradictory. This review focuses on the essential coordination chemistry and biochemistry that relate transition metal ions iron, copper, and zinc to β-amyloid (Aβ) and most likely define the peptide's roles in neurons. The metal-Aβ interactions have elements of both gain of toxic function, as usually considered, but also loss of natural functions, as emphasized in this review. Both these aspects and their relationships are discussed and their implications for future therapeutic strategies are outlined.

***Keywords*: Alzheimer's disease; β-amyloid; zinc; copper; iron; oligomer**

List of abbreviations

$A\beta_{1-40}$	β-amyloid, 40-residue isoform
$A\beta_{1-42}$	β-amyloid, 42-residue isoform
$A\beta_{1-42}/A\beta_{1-40}$	Ratio between levels of $A\beta_{1-42}$ and $A\beta_{1-40}$
ADAM	A Disintegrin And Metalloprotease, zinc peptidases, some being α-secretases
AICD	APP intracellular domain, product produced after cleavage of C99
APP	β-Amyloid Precursor Protein
APLP2	Amyloid precursor-like protein 2
ApoE4	Allele 4 of the apolipoprotein E
BACE1	β-site APP cleaving enzyme 1 (β-secretase), aspartyl protease that cleaves APP

C99	C-terminal 99-residue fragment produced upon cleavage of APP by β-secretase
CD	Circular dichroism
CSF	Cerebrospinal fluid
CuBD	Copper Binding Domain of APP
EDTA	Ethylenediamine tetraacetate
EGCG	Epigallocatechin gallate
EPR	Electron Paramagnetic Resonance
FAD	Familial Alzheimer's Disease
HFIP	Hexafluoroisopropanol, $(CF_3)_2CHOH$.
LTP	Long-term potentiation, the ability of neurons to maintain signals for longer time
NHE	Normal Hydrogen Electrode
NMR	Nuclear Magnetic Resonance
NSAID	Non-steroid anti-inflammatory drug
PSEN1	Presenilin 1
PSEN2	Presenilin 2
SAD	Sporadic Alzheimer's Disease
SHE	Standard Hydrogen Electrode
SORL1	Sortilin-related receptor 1, an apolioprotein E receptor involved in AD
ThT	Thioflavin T
ZnT	Zinc Transporter Protein showed elevated activity in AD

1. Introduction

Alzheimer's Disease (AD) is the most prevailing type (60−70%) of dementia suffered by more than 30 million people across the world (~40 million dementia cases)[1][2], and with prevalence growing by ~1.5 million cases a year[3]. Clinically, the disease is characterized by first a gradual loss of episodic memory in the form of mild cognitive impairment[4–6] and then a steady and painful degeneration of cognitive skills, identity, and life quality[7][8]; the associated helplessness of patients inflicts major costs on present and future healthcare budgets[9][10]. Because our understanding of the molecular mechanisms of the disease is not very accurate, current symptomatic treatments on the market only delay disease progression by some months[9][11]. Also, the latest attempts to provide new mechanism-based medicine largely relying on an "amyloid-alone strategy", i.e. the assumption that β-amyloid (Aβ) is alone responsible for disease, have failed for reasons to be analyzed in the following[12–16].

The loss of neurons generally occurs in distinct parts of the brain, notable in the cerebral cortex and hippocampus[17]. Brains of patients with AD display several features, two of which are currently required for definitive diagnosis: deposits of senile plaques outside the neurons and neurofibrillar tangles within the neurons[6,8,18,19]. The senile plaques consist of modified[20] Aβ peptides with characteristic β-sheet-dominated fibrillar structures[21][22][23]. The neurofibrillar tangles consist primarily of phosphorylated tau protein[24][25][26]. Other prominent and consistent features of the disease include oxidative modifications of biomolecules of the brain[27][28][29], impaired ability to use glucose[30][31][32], and imbalances in the homeostasis of metal ions[33][34], notably calcium[35][36][37], iron[28][38][39], copper[40][41], and zinc[17][42][43].

Why is it so hard to find a cure to AD? The main explanation is that the disease is dreadfully complicated. It presents itself typically late in life, and under the influence of many combined genetic and life-style risk modifiers such as smoking[44], alcohol use[45][46], diabetes[32][47], body weight[48][49][50], hypertension[51], and physical and intellectual activity levels[52][53][54], and

perhaps even certain diets[55–58]. Accordingly, more than 95% of cases arise without a family history of disease, referred to as "sporadic AD" (SAD); whereas less than 5% of new AD cases can be tracked in family history as so-called "familial AD" (FAD)[59]. The complexity of the disease is also reflected in the very broad clinical spectrum that often overlaps with other forms of dementia and produces diverse clinical and molecular manifestations[6][60]. Complexity is evident from the large variations in survival times and age of disease onset even for monogenic, inherited forms of the disease and even for the same mutation[61]. The notable, but in drug development efforts grossly overlooked, fact that age is the main risk factor of the disease[62] is perhaps the strongest indicator that a single gene or event cannot explain this disease satisfactorily and that an age-dependent trigger is required to initiate disease[55][63]. These are indications (among many others[64]) why amyloid-alone therapeutic strategies currently pursued at high costs are failing, and that we must account for the age triggers in disease mechanisms and treatment strategies.

However, to identify these triggers of disease, we must first assess the dominating paradigm and the basis of most drug-discovery efforts, the amyloid hypothesis, and why it is insufficient in its current form. After this assessment follows a review of the role of metal ions as probable age triggers of AD, with a main focus on how transition metal ions define the coordination chemistry, amyloid conformations, chemical properties and biological functions of Aβ and how these functions may be addressed in future therapeutic approaches. Since other reviews have covered the separate topics in extensive detail[34,38,65–74], the purpose here is to provide a broader, up-to-date overview of these functions, including some controversies and particular attempts at unifying data. Special attention is also given to the normal and beneficial metal-Aβ interactions and their possible role in AD.

2. The amyloid hypothesis

2.1. The basis of the amyloid hypothesis. The amyloid hypothesis[75][76][77] has been dominating the field for good reasons: The senile plaques in brains of patients formed a logical basis for trying to understand the molecular cause of the disease: They resembled protein deposits seen in proteopathies such as Creutzfeldt-Jakob disease, which led to the original hypothesis that these plaques cause AD[22]. When they were shown to consist largely of a specific peptide, Aβ, the early version of the amyloid hypothesis was established[78]. Afterwards it was found that the severe, early onset forms of FAD relate directly to genetic variations that imply Aβ, i.e. the genes coding for the β-amyloid precursor protein (APP)[79] and the two presenilin isoforms PSEN1 and PSEN2[80–84]. Aβ is indeed produced from APP upon cleavage by β- and γ-secretases[85][86], and PSEN1 is the actual catalytic unit of the γ-secretase complex[87][88][89], which however also cleaves many other substrates[90][91]. Thus, the main risk genes of early-onset FAD, PSEN1/2 and APP, can be directly related to a role of Aβ in the disease.

Other genetic risk factors have been identified but they confer small risks on general populations and associate with multigenic or sporadic forms of AD. Most notably, the apolipoprotein E ε4 allele (ApoE4) increases risk up to 15-fold for homozygote carriers[92][93][94], and the sorting protein-related receptor (SORL1 or LR11)[95] is downregulated in AD [96] and is a risk factor[97][98]. SORL1 may function in APP and Aβ trafficking and as an ApoE receptor, putting it in relation to the three FAD genetic risk factors mentioned above[99]. Genome-wide association studies have additionally suggested a number of other genetic variations that can increase risk of AD[82][100][101][102][103].

Accordingly, the amyloid hypothesis has become the dominating paradigm for understanding AD[75][76][104]. It proposes that Aβ has a toxic function that causes the disease, and the deposits were taken to indicate that too much Aβ was the cause of disease[14][76]. This overload version was

originally named the "amyloid cascade hypothesis" as it was assumed that an imbalance led to the gradual buildup of Aβ plaque deposits in brains; this buildup represents perhaps 6-8 years of total Aβ production[105]. This original understanding of Aβ overload has been modified, and approaches to tackle the disease within the amyloid hypothesis have changed, as discussed below.

2.2. Production of Aβ from APP. The Aβ peptides are produced by cleavage of APP by the two aspartic acid proteases β- and γ-secretase. β-cleavage first produces the C99 fragment[86][86], which then, depending on the precise cleavage point of C99, is cleaved by γ-secretase in consecutive steps[106] into Aβ isoforms of variable length and the corresponding APP intra-cellular domain AICD[88][107][108]. The Aβ isoforms finally released from the membrane typically vary in length between 38 and 43 residues[109], with $A\beta_{1-40}$ and $A\beta_{1-42}$ being the dominant forms[61][110].

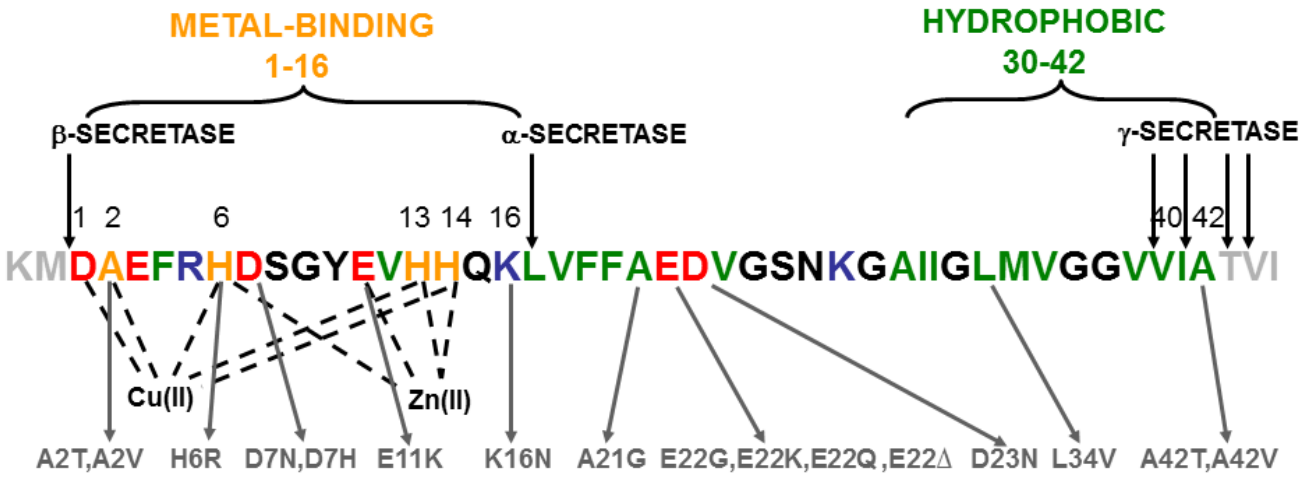

Figure 1. Aβ sequence with main cleavage and metal-binding sites. Amino acids are colored according to main metal-binding (orange), positively (blue) or negatively (red) charged, hydrophobic (green), and other polar (black). Known mutation positions are shown in the bottom.

Figure 1 provides an overview of Aβ discussed in this review, with the main cleavage sites marked. Most FAD mutations are located in PSEN1 and tend to increase steady-state $A\beta_{1-42}/A\beta_{1-40}$

isoform ratios, and this ratio is thus considered a critical determinant of amyloid pathogenicity within the amyloid hypothesis[77][111]. $A\beta_{1-42}$ has two more C-terminal hydrophobic amino acids than $A\beta_{1-40}$ and is thus more prone to aggregation[112][72] and is also more toxic to cells[75][113][114]. It should be noted that FAD-related mutations in PSEN1 often lead to lower overall Aβ levels even if the $A\beta_{1-42}/A\beta_{1-40}$ ratio increases[85][110], suggesting that the amount of Aβ is less important than the specific chemical properties of the peptides, if one wants to retain the amyloid hypothesis[61].

2.3. From quantitative to qualitative gain of toxic function. The early "cascade" version of the hypothesis has been modified, and the term "cascade" is now less used for several reasons: First, neuro-degeneration and cognitive decline does not correlate with the amount of plaques Aβ that a patient has[11,14], so the amount of Aβ cannot be the defining pathogenic feature by itself. As mentioned, AD initiates in specific parts of the brain (e.g. hippocampus) but Aβ is found throughout the brain, so there must be specific non-amyloid triggers of disease distinct to these parts[115][116]; in fact these parts fulfil special functions and are enriched in metal ions, as discussed below. Another point is that many healthy people have plaques; in fact, probably as many as 20−40% of all cognitively normal people have Aβ plaques enough[117] to be diagnosed with AD even if they are not sick[118][119]. This suggests that the plaques themselves are not pathogenic, but possibly represent pre-clinical disease states[120]. The fact that the plaques are insoluble extracellular deposits further speaks against their direct pathogenic role[64]. Accordingly, Aβ variants that predominantly form fibrils characteristic of plaque morphology, as measured by Thioflavin T (ThT) fluorescence, tend to be less severe than variants that produce other types of aggregates and oligomers[61].

Thus, while senile plaques are suggested to indicate intra-neuronal Aβ imbalances[121,122], soluble oligomers are known to be more toxic forms of the peptide and are considered culprits of the disease and increasingly targeted[123][124][125][126][127]. Plaque deposition could then in fact be a protective pathway whereby Aβ is exported from cells and aggregates into fibrils, to reduce the burden

of intracellular oligomers[113][128]. Thus, the amyloid hypothesis now centers mainly on specific, qualitatively altered forms of the soluble peptide oligomer pool, as emphasized by the $A\beta_{1-42}/A\beta_{1-40}$ ratio, rather than quantitative overload *per se*[13][110]. Most PSEN1 mutations increase the $A\beta_{1-42}/A\beta_{1-40}$ ratio[129][130][131][132], by affecting the precision of the step-wise APP cleavage[106][133][134]. However, some recent clinical tests still use reduction of plaque load as a success criteria[135].

Aβ is a many-faced molecule, and its aggregation propensity as well as measured cell toxicity is very structure-dependent[136][137][138]. Although it is increasingly clear that the bioactive forms are low-molecular weight oligomers[139], it has not yet been possible to identify the bioactive modes of the peptides that allegedly cause AD[140][141]. Correlation of structural ensembles of genetic Aβ variants to their toxicities data suggests that hydrophobic, exposed parts relate to toxicity[114]. Several toxic modes of Aβ have been suggested[73], notably induction of oxidative stress[142], impairment of long-term potentiation[143] peptides, formation of membrane channels that leak calcium[144][145][146][147], and impairment of the respiratory systems of mitochondria[148][149][150].

2.4. The "amyloid-alone" drug development crisis. Following the principles of the amyloid hypothesis, drugs have been pursued that prevent the formation of Aβ or, more recently, soluble oligomers, the inferred pathogenic Aβ species[151], either by direct molecular interaction with Aβ species[152][69][153] or by inhibition of Aβ production[107][154]. Consistent with the evidence discussed in this review, both Aβ antibodies and γ-secretase inhibitors have been ineffective or even produced adverse cognitive effects in clinical trials, despite being able to reduce Aβ load in preclinical tests[16][122]. Aβ immunization with AN1792 can lead to brain inflammation and cognitive decline[155] and no favorable Phase 3 outcomes[156]. Solanezumab showed no improvement in cognitive function in the two major phase 3 trials[157], but a subsequent positive effect after pooling

data[158][159], yet the program was abandoned in late 2016. Bapineuzumab did not show any benefits[160] and can also produce adverse effects[161] *despite* lowering amyloid levels[162]. γ-secretase inhibitors (Avagacestat, Semagacestat) that reduce the production of Aβ from APP produced adverse cognitive side effects and were discontinued[163][164].

These results are not surprising if fibrillar deposits of Aβ are downstream of the true pathogenic events or perhaps even a protective measure against intracellular oligomer (or metal) overload. Combined with the fact that many AD-causing mutations display reduced Aβ levels[165], and the many reports that physiological concentrations of $A\beta_{1-40}$ are beneficial to the brain[166][167][168][169][170], it is surprising that one-sided efforts to simply reduce Aβ levels *per se* were ever considered meaningful strategies. Yet proponents of the amyloid-alone scenario suggest that the failure of γ-secretase inhibitors is due to adverse effects of reducing other γ-secretase functions, and the failure of antibodies is excused by not having targeted the right Aβ forms[12,122]. Thus, rather than accepting that amyloid-alone therapies are not going to work because the age-trigger is missing, more resources are spent at the moment of writing to pursue modulation of the $A\beta_{1-42}/A\beta_{1-40}$ ratio and the supposed pathogenic oligomer species[85][110][154]. These expensive excursions will be at best marginally effective, because Aβ, no matter what form it has, cannot cause AD alone. Aβ is surely toxic to cultured cells at micromolar concentrations, but the instantly induced toxicity is quite distinct from the gradual AD of an aging human brain, where Aβ is present in neurotrophic nanomolar amounts[64]. Aβ does not cause disease by itself because AD starts only with age and in specific parts of the brain; it has a therapeutic window and requires, if it is causative at all, an age-trigger that chemically modifies it[64]. These trials tell us a lot about drug development strategies of pharmaceutical companies, something about the dogmatism of scientific paradigms, but unfortunately little about the etiology of AD.

The question is then, what is missing in the equation. AD is triggered by age and initiates in specific parts of the brain that are rich in metal ions, whereas Aβ is found in many parts of the brain[3]. As summarized below, the age trigger of AD is plausibly a combination of oxidative stress and metal ion dyshomeostasis which increase with age[62] and the role of Aβ in this dyshomeostasis is many-sided.

3. The evidence for a central role of Cu, Zn, and Fe in Alzheimer's disease

3.1. Cu, Zn, and Fe ion levels in AD patients. Dyshomeostasis of "natural" calcium, zinc, iron, and copper levels is a well-established feature of AD[34][38][43][171–177]. The homeostasis of the metal ions is strongly connected and delicately tuned because of the small variations in concentrations needed to shift from beneficial to toxic effects within cells[178][179][180]. These metal ions serve in neuron signaling, apoptosis, inflammation, oxidative stress control, and cell proliferation[181–186]. Both zinc and copper play distinct roles at the synaptic cleft[33,172,187,188]. The role of copper is relatively underappreciated, yet data imply a central role of prion protein and Aβ in regulating copper levels at glutamatergic synapses[33,172,189], with resting $[Cu^{2+}] \sim 1$ μM and peak levels 10−100 times higher[190]. Intracellular Cu(II) and Zn(II) levels are tightly regulated to levels as low as 10^{-18} M and 10^{-15} M[17,191], respectively, whereas vesicular zinc levels can reach $10^{-4} - 10^{-3}$ M levels[17,187,188].

Fueling the idea that metal ion homeostasis played a role in AD were early observations of tangle and senile plaque pathology of people suffering from lead poisoning[192][193]. The involvement of zinc in AD was suggested by Burnet in 1981[175]. Aluminum, manganese and iron induce tangle pathology[194][195], and aluminum was suggested to play a role in AD[196]; this role has since then been disputed[197][198], and the reader is referred to other reviews for this topic[199–202]. Like aluminum, calcium is very oxophilic and thus preferably binds to oxygen-donor

ligands[203] and is generally not associated with the N-donor ligands of Aβ. However, Aβ has been associated with calcium through its role in forming calcium-penetrable membrane channels[204–206]; calcium's extensive role in AD is reviewed in detail elsewhere[35][174][206]. This review concerns the transition metal ions zinc, copper, and iron, which have natural beneficial functions in the brain, documented interactions with Aβ, and bridge between the amyloid and metal ion hypotheses of AD *via* the distinct functions of metal-Aβ complexes.

Zinc and copper are not very oxophilic and iron is moderately so; these metals often binds to nitrogen- and sulfur-donor ligands but can also bind oxygen donors[203]. Zinc is redox-inactive as it always occurs in the symmetric closed-shell d^{10} state and as a redox-innocent conformational regulator plays a central role in DNA transcription, apoptosis, glucose metabolism, oxidative stress, immune defense, neurogenesis, and synaptic plasticity[207][187]. With this monumental importance of zinc to neurological processes, it is not surprising that its disturbance, either directly or *via* its antagonistic relationship with copper homeostasis, plays a role in many neurological disorders[187][38,65,208]. Iron and copper are redox active as Fe(II)/Fe(III) and Cu(I)/Cu(II) redox couples and are at the center of active sites of many proteins, often with functions relating to oxygen management, oxygen-activating enzymes, and electron transfer proteins[209–212]. The general homeostasis of these three metal ions in relation to AD has been extensively reviewed and is not discussed here[17,38,42,213,214].

The substantial enrichment of copper, zinc, and iron in senile plaques[215] implicated metal ions in the aggregation process of Aβ. Interestingly, the toxic gain of function assumed for Aβ rested initially on the interpretation of the plaques as overload[22], but the same argument can be applied to metal ions, since these are elevated in plaques vs. global levels in the brain[216]. This implies a potential role of Aβ production and cellular export as a mechanism of disposing excess metal ions[3].

Table 1 gives an overview of reported metal levels in AD samples vs. age-matched control samples. It is well-known that metal status varies substantially between different parts of the brain[217][218]. The nature of the deposited metal may also differ, as e.g. iron is found sometimes in a mineral magnetite-like form in brains, somewhat similar to that found inside ferritin[219][220]. The heterogeneous data can be reconciled by a time-dependent pathology of a progressive depletion of functional zinc from *bound* pool in proteins in distinct brain parts (represented as Zn(II) in active sites of proteins with typical $K_d < 10^{-7}$ M) to the *free* pools (represented as solvated, labile Zn^{2+} with typical $K_d > 10^{-6}$ M)[17]. Similarly in the case of copper, one must distinguish between copper bound to ceruloplasmin and free copper[221]. Thus, in hippocampus, amygdala, putamen, and to some extent plaques, metal ion levels are significantly changed. In the general neuropil (the unmyelinated parts of neurons and glial cells) and the general cortex, due to heterogeneity of compartments and tissue, changes will not appear significant. Due to the constant redistribution and flow from functional bound to free pools over the course of the disease, changes in peripheral tissue (CSF, blood, and hair) will not appear significant[17]. Instead, zinc tends to be deposited in local areas, notable with senile plaques, around impaired blood vessels, and in cells with tau pathology[222], with significantly increased levels in hippocampus where AD initiates[223][224][225]. Although compositions in hair and nails have been generally inconclusive, a recent report suggests significant differences in the levels of copper, iron, and other metals in nails and to some extent hair of AD patients vs. control groups[226].

Consistent with these changes, AD patients have been found to suffer a functional zinc deficiency and potential copper overload[221][227][228]. The inverse relationship between copper and zinc in the metal-rich hippocampus and amygdala is in this context notable (Table 1); the antagonistic relationship between copper and zinc levels mediated by metallothioneins is well-established[229][230], and this relationship seems important to AD, where the Cu/Zn ratio may play a central role, and metallothionein I and II are upregulated[3,17].

Table 1. Reported metal levels in AD vs. age-matched non-AD controls (↑ higher, ↓ lower, ~ not statistically different).

Part of brain	Cu	Zn	Fe
Hippocampus	↓[208]	↑[208,217,223]	↑[208]
Amygdala	↓[208]	↑[208,217,223]	↑[208]
Putamen	↑[217]	↑[217]	
Senile plaques	↑[215]	↑[215][222]	~[215]
General cortex	~[231]	↑[231], ↓[232]	~[222][231]
CSF	↑[233][234], ~[235][236]	↑[234] ~[236][237]	~[234][235][236]
Blood	~[57][236][238][239], ↓[240][241], ↑[242]	~[235][236][238][239], ↓[57][240][243][244]	↑[238], ↓[233][240], ~[57][236]
Hair	~[239][245]	~[239]	~[239]

3.2. Cu, Zn, and Fe transport and storage proteins are abnormal in AD patients. Metal dyshomeostasis is also evident from distinct changes in metal transport proteins in AD. It is notable that APP/PSEN1 mutant expressing mice also show such changes[246][247], i.e. there is a relationship between Aβ and metal status. Zinc is abundant in vesicles of zinc-enriched neurons and transported by ZnT transporter proteins[248][249]. Some ZnT[246][250] and metallothioneins (isoforms I and II)[251] are known to be upregulated in AD patients, whereas other ZnT forms are down-regulated[252]; metallothionein III which differs substantially from isoforms I and II and is brain-

specific[253], tends to be down-regulated[17]. ZnT3 knockout leads to reduced plaque burden, showing that plaque formation relates to zinc status[254]. ZnT3 knockout produces age-dependent cognitive deficits in mice[250]. Changes in the iron binding proteins ferritin[255], iron regulatory protein[256], p97[257], and transferrin[258] have all been associated with AD, and magnetic resonance imaging shows that ferritin iron is increased in hippocampus of AD brains[259]. In Menkes and Wilson's diseases copper transporting ATPases Atp7a and Atp7b are impaired to cause copper deficiency and copper overload, respectively, in neurons, with resulting neuropathological consequences[213][260][261][262].

A causative relationship between AD and metal ions is not immediately clear from genetic risk factors, because the function of APP and PSEN1 is not clearly established. However, evidence suggests that APP and PSEN1 work together in balancing intra-neuronal metal ion levels, and while PSEN1 seems to serve in calcium[263,264] and zinc/copper regulation[246][265], APP could be the "missing" copper transport protein of neurons[108,266], and APP and Aβ work to reduce brain copper levels[267], as discussed in detail below.

3.3. Cu- and Zn-interactions define APP function. APP has well-established copper and zinc binding sites[268][269][270][271]. The extracellular part of APP constitutes the major part of the protein and is divided into two domains, E1 and E2. E2 contains several metal binding sites that can regulate the conformation and possibly function of APP[272][273] (Figure 2A). E1 contains the growth-factor-like domain with the heparin binding loop[270] and the copper-binding domain (CuBD)[274][275]. The latter contains a copper binding site consisting of His147, His151, and Tyr168[276][274] (Figure 2B). The copper affinity of APP has been reported to be ~10^{-8} M[269]. There is also a Zn(II) site within residues 181−200[277]. APP has been shown to reduce Cu(II) to Cu(I) in association with electron transfer and disulfide bond formation[278]. This could imply that APP transports Cu(I) across the membrane in analogy to plasma membrane copper transporter Ctr1, which is

cleaved from the cell membrane if copper levels are elevated[279]. In this context, it is notable that knockout of APP leads to reduced copper toxicity in neurons[280], i.e. APP is involved in neuronal copper uptake. Overexpression of APP causes intracellular copper deficiency, and overexpression of the C-terminal domain of APP, C99 (which includes Aβ) causes copper and iron depletion in mice[267]. The CuBD of APP reduces toxicity from copper exposure[281].

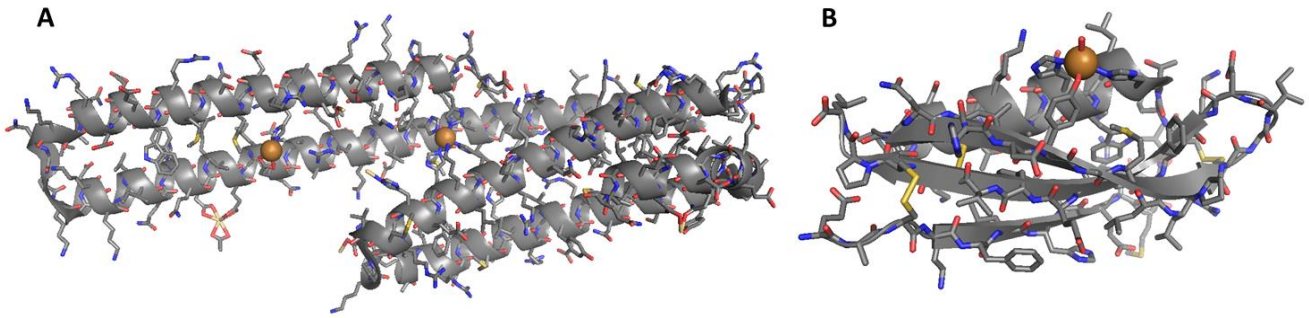

Figure 2. Extracellular copper binding sites of APP, with copper shown as orange spheres: A) Copper/zinc sites in the E2 domain of APP (PDB ID: 3UMK)[272]; B) The CuBD site of the E1 domain (PDB ID: 2FK1)[276]. The Figure was made using Pymol.

3.4. Aβ balance is controlled by Zn(II) and Cu(II). Zinc exerts a direct control over the Aβ balance both in terms of production and degradation via zinc peptidases[17]. Cleavage of APP at the α-cleavage site, which lies within the Aβ region of APP and thereby prevents Aβ production, is catalyzed by various zinc proteases of the ADAM family (A Disintegrin And Metalloprotease family)[282][107]. Several of these membrane-bound proteases, specifically, ADAM9, 10, and 17, possess α-secretase activity[283][284][285]. They work by hydrolyzing peptide bonds of Aβ, most notably between residue 16 and 17, intriguingly at the intersection of the hydrophilic and hydrophobic parts of the proteins and at the end of the metal binding region of Aβ[286]. The fact that α-cleavage causes this particular division of Aβ is probably not coincidental although so far not discussed in the literature. However, it

fits the recent suggestion that APP/Aβ work together as a Cu/Zn regulating system[3], and one can speculate that the purpose of α-cleavage is to retain the metal binding capacity of APP within the cell membrane, whereas β- and γ-cleavage makes the metal binding peptide exit the neuron.

Aβ is degraded by several different proteases[287]: Neprilysin[288][289], angiotensin-converting enzyme[290], matrix metalloproteases[291][292], and insulin degrading enzyme[293][294] are among the most prominent. These are, coincidentally, all zinc proteases. In case of functional zinc deficiency, these various zinc proteases that reduce Aβ levels could be impaired[295], both by shifting towards the amylogenic pathway and by increasing the life time of Aβ peptides[17].

β-site APP cleaving enzyme 1 (BACE1, β-secretase), the aspartyl protease that cleaves the N-terminal of Aβ from APP[296], contains a conserved copper binding site[297]. APP expression and Aβ formation is increased upon copper exposure by means of a copper sensing protein CUTA that interacts with the β-cleavage site of APP[298]. The N-terminal of Aβ, which initiates the metal binding, is incidentally also the β-cleavage site that has been shown to regulate β-secretase cleavage of APP[299].

3.5. Cu/Zn status is controlled by Aβ levels. Aged mice exposed to copper accumulate Aβ and display reduced levels of low-density lipoprotein receptor-related protein 1 (LRP1)[300], a known transporter of Aβ [301] that is also involved in APP trafficking and processing[302][303]. APP processing and Aβ production becomes more pronounced under the influence of high copper levels[304], and zinc overload increases the extend of APP cleavage and extracellular metal-enriched Aβ deposits[305]. In the light of these observations, the ability of metal ions to bind and induce Aβ aggregation[34,306–309] should perhaps be taken as indication that a natural function of metal export is associated with Aβ. A range of other observations, reviewed elsewhere[3], further emphasize that APP and Aβ not only regulate zinc and copper levels, but that the reverse is also true, implying a tightly regulated metal transport function of APP/Aβ. Accordingly, not only a pathogenic, but also a normal functional mode of Aβ-metal interaction will be discussed below.

Many other data than those listed above support a role of metal ion dyshomeostasis in AD; these are reviewed elsewhere. A few notable examples include the direct relationship between zinc and tau structural integrity[310–312], with zinc dyshomeostasis capable of aggravating tau toxicity[310,312], and the role of presenilins in maintaining zinc and calcium homeostasis[246][313], although outside the scope of this review.

4. The structural chemistry of Aβ

4.1. Aβ monomers. The structural chemistry of Aβ has been reviewed previously[3,23,314,315]; here, the main points and some additional observations will be discussed. There are several isoforms of Aβ, depending on the nature of APP cleavage, and this by itself has important implications. However, for the sake of brevity, the following focuses on the two isoforms $A\beta_{1-40}$ and $A\beta_{1-42}$ that constitute most of the nanomolar levels of Aβ found in brains and cerebrospinal fluid (CSF)[316][317]; $A\beta_{1-40}$ is in excess in CSF by a factor of 100−1000[318]. In CSF of AD patients, $A\beta_{1-42}$ tends to be selectively reduced vs. controls[318] and this feature has been suggested as a biomarker of AD[319][320]. Both the $A\beta_{1-40}$ and $A\beta_{1-42}$ monomers are dominated by random coil segments in their typical ensembles[321–323]. In water, the Aβ monomer has a coil-dominated ensemble with 5−20% helix and 0−15% β-strand[323–326](Figure 3A); as the dielectric constant of the solvent decreases in co-solvents or micelles, the helix content increases (Figure 3B), as seen from available nuclear magnetic resonance (NMR) and circular dichroism (CD) spectroscopic data and reflected in structural models with PDB codes 1BA4[327], 1IYT[324], 2LFM[321], 1Z0Q[325], and 1AML[328]. In the NMR structures of Aβ in membrane-mimicking chemical environments, the C-terminal of Aβ adopts an extended, potentially membrane-spanning helix, which fits well with the widely documented membrane channel properties of Aβ[145,146,204,329–331]. A recent structure of Aβ bound to a lipid bilayer surface indicates

formation of a characteristic fold of Aβ upon membrane interaction, with the central part being helical and the membrane-aligned hydrophobic C-terminal part being disordered[332]. Secondary structure also changes depending on chemical conditions such as solvent type, co-solvation of small molecules such as HFIP, ionic strength, and pH[333], and perhaps even their distinct tautomeric states[334].

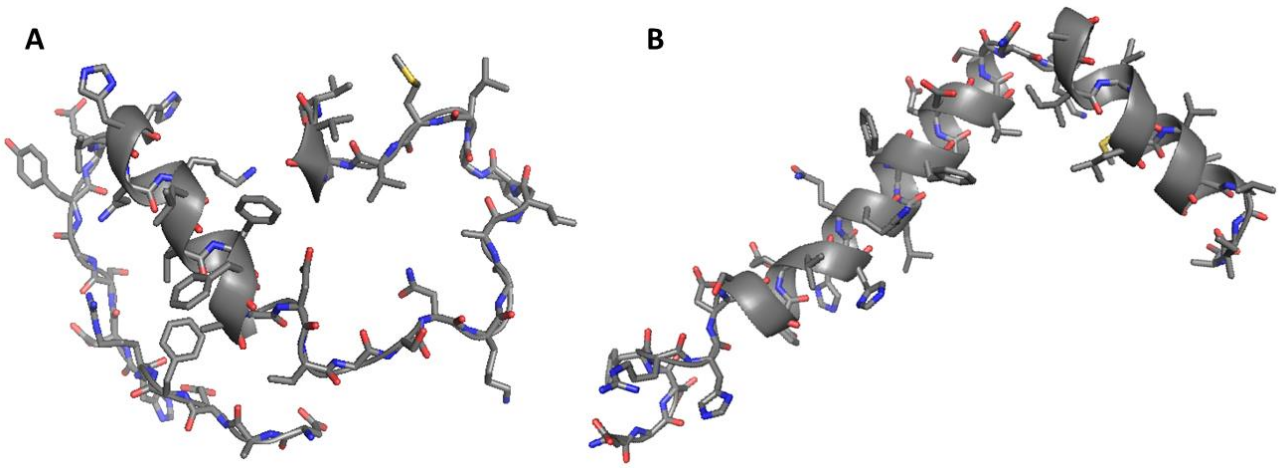

Figure 3. Different NMR structures of Aβ: A) NMR structure of $A\beta_{1-40}$ in water (PDB ID: 2LFM)[321]; B) NMR structure of $A\beta_{1-42}$ in an apolar environment (PDB ID: 1IYT)[324].

Aβ is a characteristic amphiphile: It is divided roughly in two parts of similar size, a hydrophilic N-terminal region and a hydrophobic C-terminal region[17]. This specific feature is probably not coincidental and fits well both with its position in the membrane region of APP and with the suggested function of Aβ as a cross-membrane metal transport peptide[3]. Apo-Aβ carries a charge of −3 at physiological pH. Due to the three histidines, the isoelectric point is at relatively low pH, so at physiological pH the peptide in its unmodified form, in particular in a crowded or low-dielectric environment within the neuron, will be unlikely to aggregate, as seen also from the strong helix character in such structures. However, binding of metal ions of positive charge +2 or +3 would change

the isoelectric point to close to neutral pH which provides a simple rationale for the role of metal ions in modulating Aβ structure and aggregation.

The addition of hydrophobic residues to the C-terminal of Aβ causes $A\beta_{1-42}$ to be substantially more aggregation-prone than $A\beta_{1-40}$,[335] and it is more toxic to cultured neurons[336]. Most mutations in PSEN1, the major genetic risk factor of FAD, increase the $A\beta_{1-42}/A\beta_{1-40}$ ratio while in many cases lowering the absolute levels of both isoforms. Whereas $A\beta_{1-42}$ tends to be enriched in extracellular fibrils, inside neurons, $A\beta_{1-40}$ makes up the large majority of produced Aβ, although the isoforms are later processed and modified by various peptidases[337].

The structural variability of Aβ should pose a concern, considering that the cytoplasm of neurons is molecularly crowded and quite distinct from typical buffered solutions. Identifying the physiologically relevant conformations of the Aβ monomer is a necessary prerequisite to understanding its oligomerization and natural roles in cells as distinct from *in vitro* solutions[61,72,75]. Correlation of different monomer ensembles against clinical severity of Aβ-variants indicate that specific exposed parts of the peptides correlate to clinical severity and toxicity but only in structural ensembles representative of disordered Aβ in water (as in 2LFM.pdb[321]) or helical Aβ interacting with membranes (as in e.g. 1IYT.pdb[324])[113,114,333]. This suggests that the ensemble enforced by the environment defines the pathogenicity of the peptides. These environments change the helix propensity and aggregation, which involves a transition from helix/coil to strand[325]. Studies of Aβ that mimic an intracellular environment e.g. by use of co-solvents or micelles and compare these to normal buffered aqueous solutions should thus be encouraged.

Because of the structural variability of Aβ, the secondary structures produced by molecular simulation are very dependent on choice of force field, since commonly used force fields display large differences in secondary structure propensity[338–340][341]. These effects seem to be ignored, giving the impression that most force fields are in agreement for this notoriously multi-structured

peptide[342]. A systematic analysis of Aβ structures produced by various force fields revealed major differences in strand-coil-helix balance[323], with e.g. different OPLS versions providing essentially unstructured ensembles and Amber and Gromos force fields favoring helix and sheet, respectively, with none of these capable of producing a realistic ensemble in agreement with experimental NMR and CD data[323]. These findings for Aβ fit well the general tendencies of the force fields[338–340,343], yet with dozens of theoretical studies using unbalanced force fields to study Aβ, it is perhaps not surprising that such insights have been difficult to publish. Accurate force fields[323] for Aβ include Charmm22*[344][345] and Amber99sb-ILDN[346], which have been designed to address secondary structure balance critical to disordered proteins and peptides. Amber99sb-ILDN, probably for this reason, provides significant correlation between computed structures and experimental toxicities of genetic Aβ variants, with EC_{50} values correlating with the extend of hydrophobic exposure[113][114].

4.2. Aβ oligomers. If Aβ monomers encounter each other under conditions of high concentration or contact with seed particles such as dust or trace metals in glass ware[172,306–308,347] or if the peptides are chemically modified e.g. by mutation[348][349], they tend to aggregate. In some cases, they can be induced to form distinct soluble oligomers, which may eventually (but not always) lead to fibrillar aggregates observable in ThT assays[350]; these oligomer structures are increasingly perceived to be main culprits of the disease[140][121,144,351]. After the discovery that Aβ oligomers inhibit long-term potentiation[143], trimers have been particular implicated as they completely inhibit long term potentiation whereas other sizes of oligomers did only partly so[137]. Dimers have been obtained directly from AD brains showing that these species exist in the brain[352].

Starting from a monomer structure having mostly coil, short segments of helix, and little β-strand, β-strand builds up over hours and days[353]; the β-strand character increases with the order of the oligomers[354][355]. However, the smaller oligomers formed directly from fresh monomers retain a large degree of disorder: A recent study used a range of NMR strategies, including proton-proton

dipolar couplings, to identify small (5-10 nm) non-fibrillar Aβ oligomers with turn- and coil-dominated structures[356].

Thus, pathogenically relevant oligomers are probed not by high ThT response but rather by relatively weak early ThT responses during the nucleation phase; more pathogenic Aβ species would then be expected to have more pronounced or longer life times of these states. To separate them from structures that are on the reaction coordinate towards fibrils requires additional assays that discriminates other aspects of the morphology than sheet formation. Because of the mechanism of oligomerization, a partially aggregation-prone structure with exposed hydrophobic parts and some strand features can seed other innocent helix-containing and non-stranded normal monomers[357]; it is assumed that this involves the combination of two strands by a β-turn[358]. This mechanism resembles the nucleation phase of standard fibrillation kinetics except that the seeded oligomers may become morphologically distinct from other aggregates on the fibrillation reaction coordinate.

4.3. The fibrillated peptides. This fibrillar structure is most pronounced in the aged aggregates of the peptide that mostly resemble the senile plaques found in patient brains; these structures can be both of the parallel β-sheet type, as commonly found[315], or of the anti-parallel type, as seen in some variants such as the Iowa mutant[359]. These structures are generally monitored by ThT fluorescence as discussed below, but will also show up in other assays testing for aggregates, whereas other aggregates can be silent in ThT assays[360].

Plaque deposits are probably nonpathogenic: Many cognitively normal people have such deposits[117][118][119], and their local deposition does not correlate with cognitive decline[115][116]. The tendency to form fibrils of Aβ variants does not correlate with a variant's clinical severity[61], and plaques, which are extracellular insoluble deposits of Aβ, are not very toxic, whereas intracellular soluble oligomers of Aβ are[123][124][125][126][127]. In contrast, a high plaque load may in some people indicate protective ability to export pathogenic forms of Aβ from cells[113][128].

4.4. Aggregation propensities of Aβ peptides studied by thioflavin T assays. The conceived importance of Aβ aggregation to the pathogenesis of AD has led to many studies on the aggregation propensities of Aβ peptides. These aggregation propensities are often measured on Aβ samples (full-length or truncated wild-type, mutant, or otherwise modified peptides) in a presumably monomeric state by monitoring the sigmoidal increase in the fluorescence of the benzothiazole salt thioflavin T (ThT) over time as a proxy of aggregation[361]. If the peptide forms fibrils, it usually does so only after a period of some hours, the nucleation (or lag) phase. When fibrillation starts, this is monitored as a sharp increase in fluorescence intensity, the elongation phase, that saturates once the maximum length and fully fibrillated structures are obtained.

The ThT responsive structural elements are mostly of the β-sheet type, although other structural features may contribute to the fluorescence as the quantum yield of a fluorophore depends on the local geometry[362][363]. It is well-known that ThT assays on various prepared samples show remarkably different results[364][365], and conclusions have differed over the relative aggregation propensity of Aβ variants, because of variations in protocols[366][367]. Often $A\beta_{1-40}$ is used due to its smaller aggregation tendency and thus more time-resolved, reproducible behavior. Also, it has been reported that recombinant and solid-state synthesized Aβ do not aggregate in the same way[368], and synthetic and extracted Aβ also behave differently[369], whether because of different types of impurities or because the peptides themselves may be different. For this reason, further comparative studies of recombinant and synthetic Aβ are encouraged. These issues are related to Aβ's extreme sensitivity to changes in chemical conditions and environments[323], and this renders reported properties such as aggregation propensities exceedingly dependent on sample preparation and chemical context[370], as well as the time scale of the experiment[113][371], a major problem in the field that needs to be solved[372][373][374]. Notable issues include:

1) The peptides may not be distinctly monomeric; if so, lag phases tend to appear shorter and ThT absorbance curves may not be comparable between studies[111]; this can be due to trace pollutants, notably dust and trace metals in glass ware[375][376] or modified peptides or other molecules that function as aggregate seeds[335,377][364]. Thus, glassware must be analytically clean, using preferably multiple cleaning strategies including strong acid. A typically used monomerization agent is hexafluoroisopropanol (HFIP), which must however be removed carefully to prevent interaction during the ThT assay; another approach is to use strong base; shaking and other perturbations of the sample may also produce seeds.

2) There are multiple ThT binding sites in amyloid structures, and therefore they may differ between different morphologies; this makes it hard to interpret the morphology from a single ThT fluorescence signal[378]. Also, ThT mainly measures fibrillar aggregates rather than other types of aggregates[379], although oligomers have been reported to have a ThT signature[380]. For example, the ΔE22 variant of Aβ produces fibrillar aggregates that are less ThT-responsive than fibrils of wild type Aβ[381]. Thus, weak ThT absorbance cannot be interpreted as absence of aggregates, and many of the ThT silent aggregates may be pathogenically relevant.

3) Although mostly overlooked, the ThT molecule itself may favor aggregation (for example it carries a positive charge that would render the net charge of Aβ smaller), *and it may do so differently for different Aβ variants*. When metal ions are bound, ThT will change the charge of the ternary complex from −1 to 0. Thus, future studies should use several measures of aggregation as a control of this possibility.

4) Shaking vs. non-shaking during the ThT assay will change aggregation; shaking will substantially accelerate aggregation[382], but also provide more homogeneous results; whether shaking or non-shaking is more physiologically relevant is not clear and often the type and amount of shaking is not reported despite its effect on aggregation.

5) A physiological ionic strength and pH needed, because salt and pH can affect the aggregation process, the interaction between fibrils and ThT molecules, and the ThT absorption itself[383][384].

6) Aggregation in water probably differs from aggregation in realistic cytoplasmic environments[385]. The direction is not obvious since several effects are involved[386–388]; excluded volume would favor aggregation but higher helix content of Aβ, which slows aggregation, is stabilized in low-dielectric environments[333]. Studying Aβ under "physiological" conditions clearly involves not just temperature, salt, and pH, but also a model of the intra-neuronal environment using e.g. co-solvents or crowding agents, which has so far not been studied in much detail. Probably the role of ThT responsive fibrillation has been overemphasized as the relative importance of fibrils will probably decrease in a cellular environment where helix propensity is larger.

Due to these difficulties, sample preparations can differ between studies and the reported aggregation propensities of Aβ peptides are in some cases in conflict[61].

Table 2. Clinical phenotype, aggregation propensity, $A\beta_{1-42}/A\beta_{1-40}$ ratio, cytotoxicity, and reference to metal-binding studies of genetic variants of Aβ. AD = classical AD phenotype. CAA: Cerebral amyloid angiopathy. n.s.: Not significantly different from wild-type (WT). Qualitative estimates are based on numerical data from [61] and recent updates in the literature where references are given.

Aβ variant	Clinical phenotype	Aggregation propensity vs. WT	$A\beta_{1-42}/A\beta_{1-40}$ vs. WT	Toxicity vs. WT	Effect on metal binding
A2T (Icelandic)[389]	protective[390]	↓[382][391][392] less trimers[393]	n.s.[390], less total Aβ[391]	N/A, ↓LTP inhibition[382]	N/A
A2V[394]	recessive AD	↓[382] ↑[392], forms trimers[393]	n.s.[390]	n.s.[348], ↑LTP inhibition[382]	[395]
H6R (English)[396]	AD	↑[397][349] Stabilizes oligomers[397]	n.s.[349]	n.s. but ↑oligomers[397]	[398][399][400]
D7N (Tottori)[401]	AD	↑[397][349] ↓[402] affect oligomers[397][403]	n.s.[349]	n.s.[397]	[399][400]
D7H (Taiwan)[404]	AD	↓[404] increase oligomers[404]	↑[404]	n.s.[404]	[400][404]
E11K (Leuven)[405]	AD	↑[405]	↑[405]	N/A	[400]
K16N[406]	AD	↓[406]	n.s.[406]	n.s.[406]	N/A
A21G	AD/CAA,	↓[348,402,408,409]aff	n.s.[410] ↑[405]	n.s.[411][412]	[408]

(Flemish)[407]	severe	ect oligomers[403]			
E22G (Arctic)[413]	AD/CAA	n.s.[348], ↓[402][414] ↑[409][411] Affect oligomers[403]	↓[402][411]	↑[61]	[415]
E22K (Italian)[416]	CAA	↑[348][417] ↓[402]	↓[61]	n.s.[418]	N/A
E22Q (Dutch)[419]	CAA, severe	↑[348,408,409,412,417] fibrils ↓[402]	↓[61] , n.s. 70]	↑[410] ↑[418]	[408]
D23N (Iowa)[420]	AD/CAA	n.s.[348][417] ↓[402] ↑[409][412] fibrils; anti-parallel sheets[421]	n.s.[412]	n.s.[348]	N/A
E22Δ (Osaka)[422]	AD	↓[422] less fibrils, more oligomers	n.s.[422]	↑[422]	N/A
L34V (Piedmont)[423]	CAA	N/A	N/A	N/A	N/A
A42T[424][425][426]	AD/CAA	N/A	N/A	N/A	N/A

4.5. FAD- and CAA-related Aβ mutants. The three major genetic risk factors of early-onset familial AD are inherited mutations in the genes encoding for APP, PSEN1, and PSEN2[61,83,427,428]. Most of these are located within the PSEN1 gene, but there are also more than 50 mutations associated with APP. Among these, ~15 are located within the Aβ sequence of APP (Figure 1). Since these mutations directly change the nature of Aβ, many studies have investigated how

these chemical changes affect the properties of Aβ; some notable examples of such studies are summarized in Table 2. The estimated property is given relative to the wild-type as a reference point, to enable comparison. The effect of the variant is reported as increased (↑), decreased (↓), or not significantly different from wild-type Aβ (n.s.). The data include both studies of $A\beta_{1-40}$ and $A\beta_{1-42}$ with directions reported vs. the corresponding wild type isoform as reference, based on a previous meta-analysis[61] and additional new data cited in Table 2. Clinical phenotype has been reported as AD, CAA or protective, and as severe in some cases where average age of symptom onset is particularly low[61]. Aggregation propensities are based on reported effects vs. WT in same study, from t_{lag} (short t_{lag} = high aggregation tendency). Toxicities were based on reported EC_{50} values vs. WT measured in cell viability assays[61].

As seen from Table 2, the reported properties of Aβ vary substantially due to the heterogeneity of samples and differences in applied protocols and methods; this has the important consequence that many previous reports on the disease mechanisms of single or a few Aβ variants are not very significant and may have been overemphasized. This heterogeneity applies not only to aggregation propensities measured but also to reported Aβ levels observed for each variant, and to the toxicities of the variants. Disturbingly, when considered as a whole, there is no simple "amyloid-alone" feature that explains the pathogenicity of all these variants[61]. Although not immediately clear from Table 2, there is a tendency in recent literature to report that more severe variations associate with less ThT responsive features, as seen for e.g. A2V compared to A2T and WT[382]. Another recent comparative analysis suggested that all studied variants in position 21−23 produce less ThT response over time than WT $A\beta_{1-42}$ despite forming aggregates[360]. The lack of resolved lag phases suggests seed impurities in the starting samples, so the data may not be comparable at early time points, although the variants show less ThT response also at later times. Previous work reported very high aggregation rates of these variants based on sedimentation assays[348]. These observations fit with the emerging view that ThT-

responsive structures are in fact often non-pathogenic, just like senile plaques, whereas amorphous non-ThT responsive aggregates are pathogenically relevant, as discussed further below.

Generally speaking, N-terminal mutations have been associated with clinical phenotypes that involve classical AD hallmarks, including both senile plaque pathology and neurofibrillar tangles, and in their dominant form, they tend to give relatively late-onset FAD. In contrast, the A2V mutation has been associated with early onset severe FAD in its homozygote state[394]. Mutations in the hydrophobic C-terminal part of Aβ have generally been associated with different clinical phenotypes characteristic of severe amyloid angiopathy but not tangle pathology that would classify as classical AD.

However, literature reports on the properties of these variants differ to some extent, a heterogeneity that is explained from the differences in protocols applied, in particular regarding the preparation of monomer Aβ, but also in terms of analytical methods applied[61]. It is notable that clinically severe variants such as A21G and A2V, E22Q, and E22Δ (age of symptom onset from 36−52 years[61]) have *smaller* tendencies to fibrillate than some other variants such as the English and Tottori FAD variants with 56−61 years of onset[61]; this suggests that fibrillation as measured by ThT response may not be pathogenic and perhaps even protective[61,333]. A recent study found that the larger Aβ aggregates that are less bioactive but found in AD brains can dissociate into smaller, more bioactive aggregates[139]. In contract, variants that favor formation of pathogenic oligomers on a pathway distinct from fibrillation may lead to disease, and this pathway is not well probed by ThT assays, but can be studied by other supplementary assays that probe aggregates less specifically.

Aggregation propensities of Aβ variants can be correlated against the variant's structural features. These studies suggest that general hydrophobic exposure (or, conversely, loss of hydrophilic surface area) imposed in the ensemble explains most of the trends in aggregation propensities, rather than distinct secondary structure changes in parts of the peptide[113,114]. Molecular dynamics

ensembles of the variants in Table 2 indicate significant variation in secondary structure, with helix content varying from 15–30% and hydrophobic surface area varying by 15%, features that correlate with experimental toxicities[114]. More extended and kinked helical structures of Aβ characteristic of low-dieletric environments and membranes (1IYT, 1Z0Q) reproduce experimental aggregation propensities, whereas disordered compact structures with two turns characteristic of 100% water (e.g. 2LFM) did not correlate as well with experimental aggregation tendencies, probably because the exposure is shielded in these conformations and this structure is already on path towards oligomerization[113].

5. The coordination chemistry of Aβ

5.1. Aβ interactions with Zn(II). Aβ is a genuine metal-binding peptide with an N-terminal metal-binding site constituted by residues 1−16[429][430][431], which notably include three closely situated histidines (His-6, His-13, and His-14) as well as several other functional groups that can act as ligands depending on conditions[432][66]. Metal ions mostly form 1:1 complexes with Aβ, sometimes with a secondary, low-affinity binding site[271][429][433][434][435]. One of the first studies of metal ion binding to Aβ (and two variants, E22Q and A21G) found that the peptides readily bind Zn(II) and Cu(II), but less so Fe(II) and Al(III), that Cu(II) binds more strongly than Zn(II), and that the K_d of Zn(II)-Aβ was ~1 μM. All these features have since then been largely confirmed[408]. This affinity of Aβ towards Zn(II) is similar to the affinity of two Aβ molecules[436], but also typical of non-specific weak binding[17,65].

Zn(II) is diamagnetic due to its d^{10} closed shell electronic structure and can thus not be studied by EPR. Instead, the zinc binding site of Aβ has been elucidated by NMR experiments. It features three histidines bound to Zn(II) at the same time, as well as Glu-11, to produce a distorted tetrahedral

coordination geometry with Glu-11 binding preferably with both oxygen atoms of the carboxylic group (Figure 4A)[437][438]. Different types of coordination modes have been suggested that involve also donor atoms from Asp-1[432].

The binding of metal ions to Aβ changes its structure[434][439]. The changes in structure induced by metal ions are diverse and not simply explained as induced fibril formation[440], as aggregates induced by Cu(II) and Zn(II) can sometimes also be distinctly non-fibrillar[439]. Zn(II) binding may increase the helix character of the monomer Aβ[441], a feature that would be consistent with the cross-membrane metal transport and channel formation by Aβ[146,329,442–444]. Other studies however suggest that Zn(II) disrupts helix structure of the monomer Aβ to facilitate aggregation[445], consistent α-to-β transition during the aggregation process[325][446].

Recent results suggest that Zn(II) lowers the affinity between Aβ molecules, whereas Cu(II) had little effect, so it remains an open question how the process works[436]. From a simple electrostatic point of view, the coordination of metal ions, by their reduction of net charge from -3 to -1, reduces electrostatic repulsion between the metal binding regions of Aβ while still allowing the hydrophobic parts to interact, much in the same way as a reduction in pH would do; the change in charge occurs in the same part of the peptide.

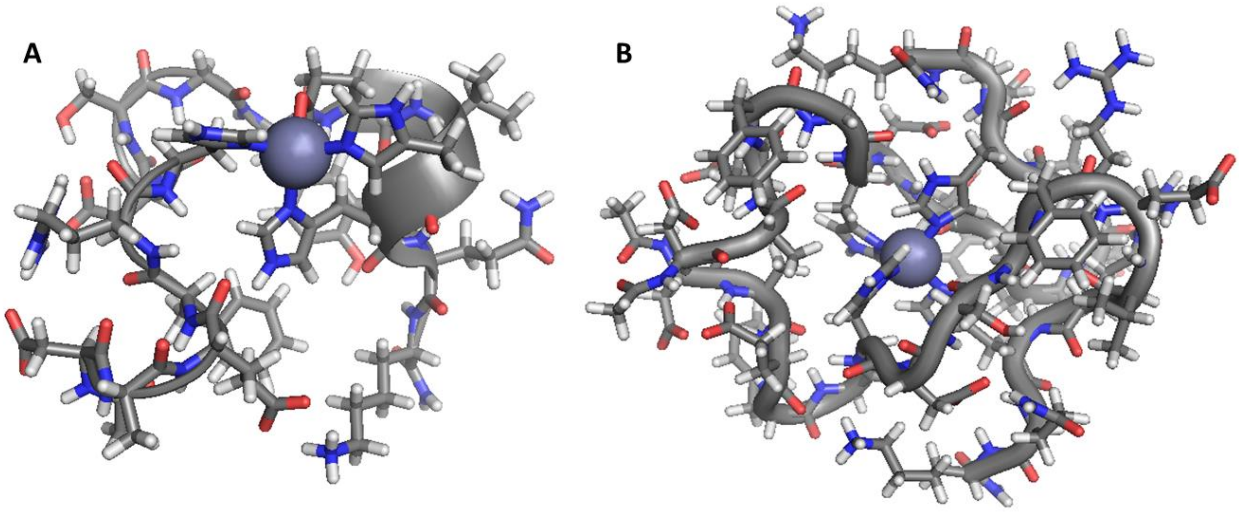

Figure 4. Coordination geometry of zinc in Aβ: A) Human $A\beta_{1-16}$ (PDB ID: 1ZE9) with 3His, 1Glu coordination mode. B) Dimer of Rat $A\beta_{1-16}$, with a 4His coordination mode (PDB ID: 2LI9)[447].

Wild-type murine Aβ contains three different amino acids within the metal binding N-terminal: R5G, Y10F, and H13R. This Aβ is less toxic and less aggregation-prone than human Aβ[448]. In rat Aβ, zinc can form a 4His tetrahedral coordination geometry that has been speculated to be protective[447], shown in Figure 4B. The dimer state is of potential importance in understanding the fast zinc-induced aggregation of Aβ, which rapidly leads to β-sheet rich fibrils[347][440].

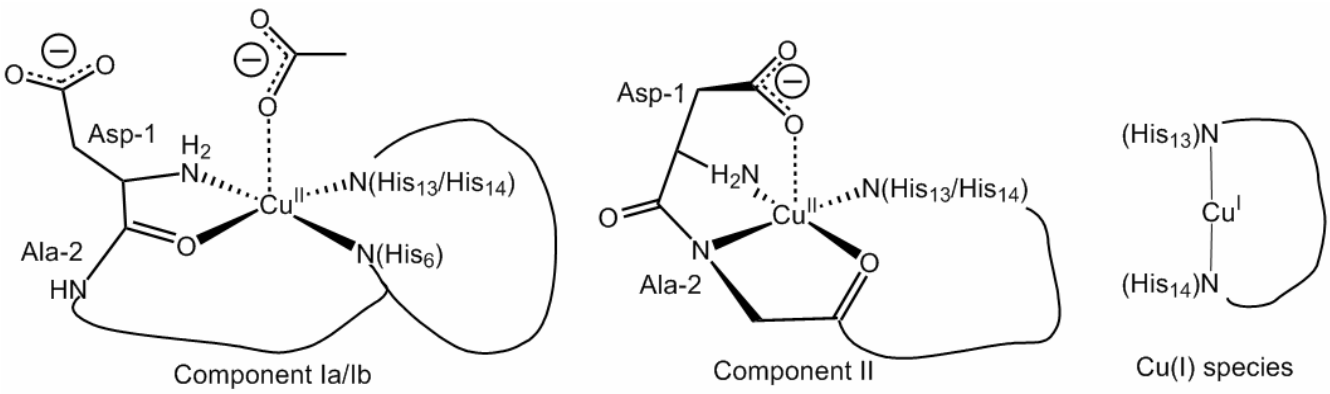

Figure 5. Proposed Cu(II) and Cu(I) coordination modes of Aβ according to Ref. [449]. The axial carboxylate ligands may be labile.

5.2. Aβ interactions with Cu(II) and Cu(I). Cu(II) has an orbitally degenerate d^9 electronic configuration, which is Jahn-Teller distorted to produce tetragonal structures dominated by the square planar coordination mode and a weak axial ligand caused by the doubly occupied d_z^2 orbital. These general considerations fit well with the typical coordination chemistry of Cu(II)-Aβ discussed below. The affinity of Cu(II) towards Aβ is relatively high, with typical K_d values of 10^{-8} to 10^{-11} M[17][435][65] although weaker binding has been reported[450][451]. Cu(II) binds more strongly to Aβ than Zn(II) by perhaps ~1000-fold consistent with the Irving Williams series[452]. Accordingly, even at Cu(II)/Zn(II) ratios as low as 1/1000, Cu(II) will determine the morphology of Aβ; in synaptic clefts, when Cu(II) reaches its peak concentrations, it may thus dominate the coordination chemistry of Aβ. $Aβ_{1-16}$ produces similar K_d as the full-length peptide, which is thus often used as a model of the metal-binding to Aβ[453]; however, any interplay between metal binding and aggregation requires full peptides due to the central role of the C-terminal half of the peptide in the aggregation process[17].

Cu(II) is known to bind Aβ using several coordination modes that depend on pH[454]; typically, these involve three N-donor ligands and at least one O-donor ligand, mostly from Asp-1 of Aβ[455]. Tyr-10 seems not to be involved in direct coordination of these two forms but could play a role in transient redox-active species[456]. The relevant N-donors include His-6, His-13, and His-14[457], a deprotonated backbone nitrogen donor, and the deprotonated N-terminal amide[66,286,449]. These different coordination modes are referred to as component I (dominating at low pH) and component II (dominating at high pH) and they differ by deprotonation a nitrogen atom, possibly the backbone NH of Ala-2, which can then serve as a ligand at higher pH[449]; the structures most consistent with current data are shown in Figure 5. The pH where these two components are of similar importance is ~7.8[399]. Component I and II are effectively distinguished by EPR spectroscopy where Component I features $g_{\|}$ ~2.27 and a hyperfine splitting constant $A_{\|} \sim 180 \cdot 10^{-4}$ cm^{-1}, vs. 2.23 and

$160 \cdot 10^{-4}$ cm^{-1} for component II[399][449]. The values for Component I are very similar to what one would expect for histidine coordinated to Cu(II), with e.g. $[Cu_2(H_2bim)_2]$ (H_2bim =2,2'-bi-imidazole) having $g_{\|}$ ~2.26 and $A_{\|} \sim 176 \cdot 10^{-4}$, similar to component I[458].

The half potential of Cu(II) reduction for $[Cu_2(H_2bim)_2]$ is approximately +0.3 V vs. SHE[458], and the half potential would be expected to be in this range for Cu(II)-Aβ. Accordingly, Cu(II)-Aβ can be reduced to Cu(I)-Aβ, and this may lead to formation of reactive oxygen species [434][459][460], a process that is partly prevented by Zn(II) interaction with the peptide[461]. *In vivo*, ascorbate is a likely provider of reducing equivalents[449]. As discussed above, Aβ is very structurally flexible; this enables full relaxation upon reduction to the preferred trigonal and linear geometries of Cu(I)[462]. The ligand donors of Cu(I)-Aβ are His-13 and His-14, as shown in Figure 5, although His-6 may also bind to Cu(I) in some conformations[66][463].

Mouse Aβ still binds copper but differently from human Aβ[464]. It has been found that while copper binding and reduction is impaired in mouse Aβ due to these substitutions, the oxidative stress inducing effects are similar[465]. Currently, the redox activity of Aβ has been viewed as a gain of toxic function. However, redox activity may also be part of the normal function of Aβ as a cross-membrane metal transport peptide, because Aβ serves a normal role in synaptic transmission[466], and reduction to Cu(I) and Fe(II) is a common feature of cross-membrane metal transport[3][262]. Additionally, the redox activity can be anti-oxidant in its nature, depending on the exact half potential and the presence of other redox active molecules such as ascorbate: Indeed, Aβ can protect against copper and iron induced oxidative stress[167][467][468]. Thus, a broader view of metal-Aβ interactions that also includes beneficial natural functions seems warranted, as elaborated further below.

5.3. *Aβ interactions with Fe(III) and Fe(II).* Iron is found co-localized with Aβ in senile plaques (~1 μM), but in amounts substantially less than zinc (up to 1000 μM)[215]. Low equivalents of iron have been obtained from metal-containing plaques[469]. Fe(III) salts can produce complexes with Aβ

aggregates[470]. The process leading to this co-localization is not entirely clear, and only a few studies have identified direct iron binding to Aβ, perhaps because Fe(II) is easily oxidized to Fe(III), and the latter tends to form insoluble salts. Fe(II) has been shown to form complexes with Aβ with primarily ligands constituted by Asp-1, Glu-3, His-6, His-13, and His-14[471]. As expected from the Irving-Williams series, Fe(II) binds more weakly than Zn(II) and Cu(II)[472], as also seen from replacement studies of isotope-labeled Zn(II[408]). It has been also found that the Fe(III) redox state is favored substantially when bound to Aβ, relative to free iron, although the affinity for Fe(II) remains much higher[473]. Given the major role of iron dyshomeostasis and systemic iron dysfunction in AD[17,28,34], more studies on the Aβ-iron connection seem warranted.

Even if iron in free form may not interact strongly with Aβ, other forms of iron could do so, and such interactions could be important modulators of Aβ structure and function. One notable interaction is between heme and Aβ which may induce functional heme deficiency[474]. Heme oxygenase, the enzyme that degrades heme, has been implied in AD[475] and is downregulated by APP[476]. Heme-Aβ complexes can be formed *in vitro* that display peroxidase activity and prevent aggregation of Aβ[477,478], as do porphyrins[479]. A likely coordination mode is achieved by the four equatorial N-donors of porphyrin, a "proximal" Fe-N bond to His-13 of Aβ, and a "distal" water molecule with a hydrogen bond to Arg-5[480]; if so, this complex is conspicuously similar to redox-active heme enzymes of the peroxidase type.

5.4. Effect of metal ions on Aβ aggregation. Metal ions have distinct effects on Aβ structure and properties, including its aggregation propensity, and due to the heterogeneity in structure and sample variation discussed above, the metal-induced effects have been very diverse, and apparently contradictory[71]. To understand this, one must distinguish at least three types of aggregates: Regular, extended β-sheet fibrils, soluble oligomers of two or more Aβ molecules, and larger amorphous non-

fibrillar aggregates. Each of these three classes of aggregates may be of variable pathogenic relevance and reflect differences in secondary structure, primary and secondary nucleation processes[481].

The first reports on the effect on metal ions on Aβ aggregation found that metal ions such as Al(III), Fe(III), and Zn(II) are strong inducers of aggregation[347][376][482]. However, the types of aggregates differ: Zn(II) and Cu(II) can inhibit formation of fibril structures, while still forming distinct non-fibrillar aggregates; with Fe(II) and Al(III) forming distinctly more fibrillar morphologies[379]. While Cu(II) produces non-fibrillar aggregates under most circumstances[483] and can induce conversion of some β-strand into helix[286] and inhibit fibrillation[484], zinc can induce both types of aggregates, although the non-fibrillar aggregates may eventually be converted into fibrils[439].

The aggregates formed by Cu(II) depend on the stoichiometry of binding[485]. Data suggest that sub-equimolar Cu(II) binding accelerates fibril formation in dilute Aβ solutions[65][486] whereas amorphous aggregates are formed when Cu(II) occupies most of the coordination sites in the various Aβ peptides, i.e. when $[Cu^{2+}] > [A\beta]$. These aggregates display different toxicities, with Cu(II) aggregates having been reported to be nontoxic[379,439] and the more fibrillar aggregates produced by Cu(II) being toxic[486]. Thus, the aggregation behavior depends not only on the Cu(II)/Aβ ratio but also on the absolute Aβ concentration[486].

An explanation is the following: In physiologically relevant dilute solutions of Aβ, pair encounters of the peptides are rare but if Cu(II) is present in small amounts, seeding will occur through electrostatic repulsion minimization that will lead to fibrils *if and only if* most coordination sites are still empty and [Aβ] is sufficiently high. Additional Cu(II) binding leads to structurally distinct monomers and dimers[487] that favor amorphous aggregates and prevents formation of mature fibril structures[488]. In disordered monomers, the metal binding is less subject to steric control, and although the Cu(II) coordination is relatively similar in fibrils and monomers[435], there is disagreement on the affinity of Cu(II) for aggregates, some reporting it similar to[435] and others 100-

fold higher than in monomers[489], as has also been suggested for Fe(II)[472]. Even modest changes in the coordination mode can change K_d by a factor of 10[490]. Small changes in affinity could have large influences on the ability of Cu(II) to visit multiple Aβ molecules and small changes in hydrophobic surface exposure will promote aggregation-prone conformations[113]. In contrast, due to the high affinity of the peptide for Cu(II), higher Cu(II) levels will increasingly lead to occupied metal sites that prevent fibril structure but may lead to hydrophobic separation and precipitation of the Cu(II)-Aβ amorphous aggregates[65].

5.5. Metal binding to mutant and modified Aβ. As described recently[61], the clinical phenotypes, aggregation propensities, produced amyloid levels, and toxicities of FAD/CAA related mutations do not provide a common mechanism of disease. For example, the $Aβ_{1-42}/Aβ_{1-40}$ ratio increases significantly vs. wild type in only two variants, D7H and E11K[61], whereas total Aβ levels increase in A2V, D7H, E11K, K16N, and A21G. These mutations all occur in the N-terminal half of Aβ that gives rise to "classical" AD phenotypes with tangles and senile plaques, as opposed to the CAA phenotypes seen for some mutations of the C-terminal half; this distinction could indicate that metal ion coordination of Aβ affects the phenotype[3].

The Aβ-overload phenotype resembles that of the Swedish double mutation just before the N-terminal of Aβ in APP, a mutation that remains widely used as a research model of AD despite its extreme rarity and distinct phenotype of increased Aβ production, which is very different from many other APP variant phenotypes and most PSEN1 phenotypes (i.e. it probes the classical overload "cascade" hypothesis which is now largely abandoned), as criticized recently[3]. The only known protective A2T variant[390] reduces Aβ levels possibly by modifying the β-cleavage site[391]. Yet the pathogenic Osaka E22Δ variant also reduces Aβ levels, and the English H6R, Tottori D7N, Arctic E22G, Italian E22K, and Dutch E22Q do not change Aβ levels significantly[61]. Similar

inconsistencies apply to toxicities and aggregation propensities, as seen in Table 2. Therefore, amyloid-alone features cannot coherently explain disease mechanisms[3,61].

Could the widely documented interaction with metal ions be the missing common denominator and at the same time, the age trigger? The metal-binding properties of some of these genetic variants have been studied, with key references given in Table 2. Mutations have been shown to modify metal binding in some cases[216,395] and can change Cu(II) affinity by several orders of magnitude[490].

The recessively pathogenic A2V mutation features a similar first coordination sphere as the wild type peptide but has some changes in the morphology beyond the first coordination sphere[395]. Cu(II) binding to the English H6R and Tottori D7N mutations have been studied with EPR and NMR[399]: Whereas D7N showed similar coordination chemistry as the wild type and a similar pK_a for conversion between component I and II (7.7 vs. 7.8 for WT), notable differences were observed for H6R, consistent with the loss of His-6 that functions as a ligand in lower-pH favored Component I (see Figure 5)[399]. The binding of Zn(II) to this mutation has also been studied and was found to facilitate dimer formation[398].

The D7H (Taiwan) mutation introduces an additional metal-binding His and is thus of particular interest as a model of metal-induced pathogenic changes to Aβ. D7H has been shown to slow fibrillation and increase the life-time of amorphous aggregates and oligomers, and equimolar amounts of Cu(II) and Zn(II) produced non-sigmoidal early amorphous aggregates of the type that are increasingly considered pathogenically relevant[404].

Electrochemical studies of Zn(II)-Aβ variants H6R, D7H, D7N, and E11K indicate a major shift towards positive redox potential in all cases[400]. This is not surprising given the loss of negative charge density of Aβ associated with +2 metal binding, which would affect the redox-active Tyr-10 situated in the immediate neighborhood of the metal ion[491][492], and potentially also the oxidation propensity of other parts of the peptide, notably Met-35[493]. Metal binding to C-terminal mutants has

also been studied in a few cases. Because these mutations are not within the metal binding site, small effects on metal binding are expected, as was also found when studying displacement of Cu(II), Fe(II) and other metal ions with radioisotopic Zn(II) bound to $A\beta_{1-40}$ WT, A21G, and E22Q peptides[408].

Various post-translationally modified forms of Aβ peptides have been observed *in vivo*. These include N-terminally modified peptides such as iso-Asp1 and D-Asp, peptides truncated from the N-terminal, e.g. $A\beta_{3-40}$, typically in a pyroglutamated form[20][494], and peptides where other carboxylic side chains have been isomerized[495]. Since these changes occur within the metal-binding site, it is of interest to understand how metal binding is affected by these modifications. Site-specific isotope labeling EPR suggests that in many of these modifications, Cu(II) binding is markedly affected as evidenced from significant changes in g-values and hyperfine coupling constants[395]. The EPR parameters obtained for various modified Cu(II)-Aβ species have been recently reviewed[67].

The pathogenic relevance of these modifications remains unclear. Probably the peptides are modified at late stages of the deposits; this reasoning arises from the fact that the senile plaques are on average several years old, because the plaque burden represents many years of total Aβ production[105]. From this consideration, one must expect that the plaque deposits are substantially modified and that this may not be very relevant but merely a consequence of chemical aging; this interpretation resonates with the increasing role played by soluble oligomers of Aβ[12,121], rather than extracellular, insoluble plaques[496]. If however N-terminal modifications occur already in solvated monomers and oligomers, they may be pathogenically relevant and their effect on metal binding would be quite important.

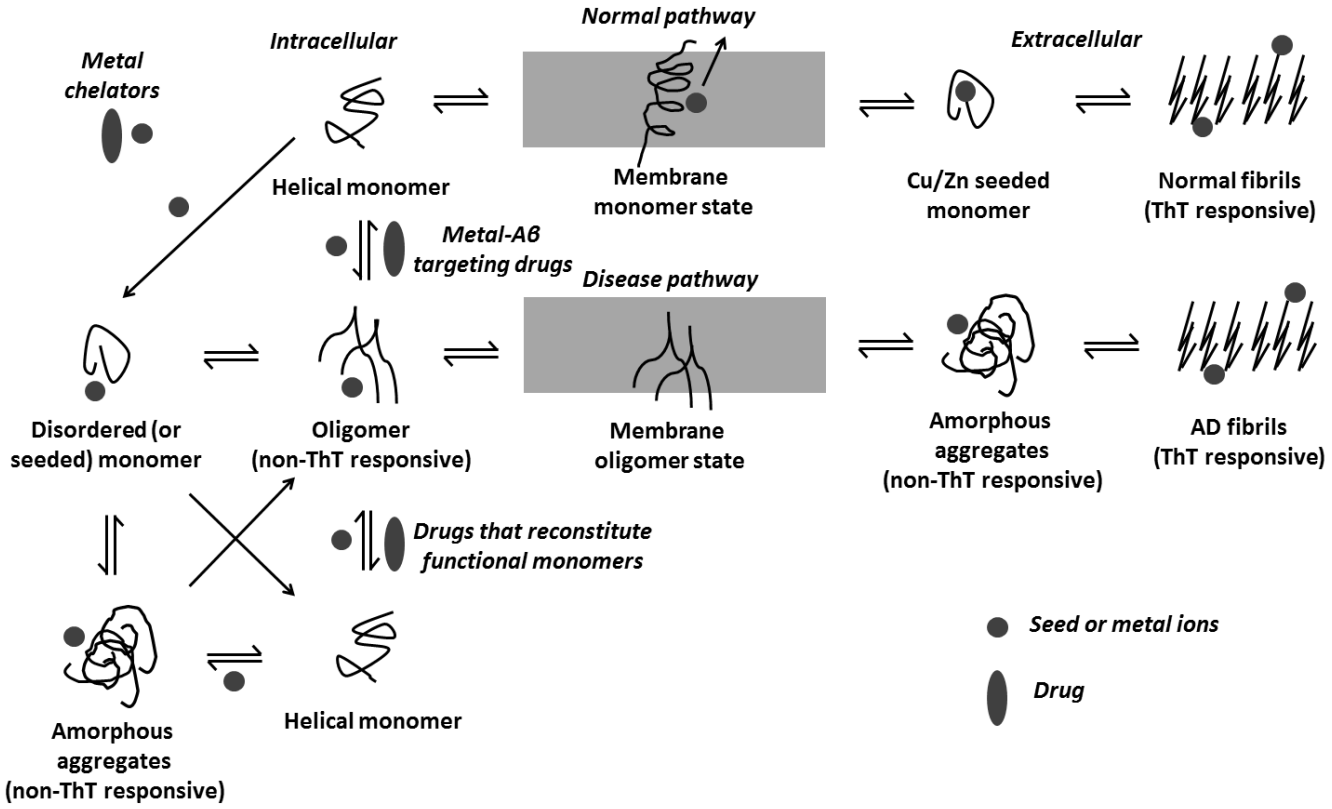

Figure 6. Overview of main pathways relating metal ion interactions to Aβ function after Aβ production. Metal ions also play a major role in controlling Aβ production itself. Emphasis is placed on both the normal physiological pathways and the pathogenic pathways of Aβ-metal interactions. Notably, mutations could weaken normal metal transport function of Aβ by changing the ratio or levels of Aβ or by directly changing the metal-binding capabilities or cross-membrane transport properties of Aβ itself, which depend on its amphiphilic nature.

6. How metal-Aβ interactions define Aβ functions

Figure 6 shows an overview of the main pathways relating to Aβ-metal interactions. The reader will be familiar with the left part of this figure. However, on the top right, suggested normal pathways of action in the reversible transport of metal ions across neuronal cell membranes have been included, viz. the natural function discussed above for the APP/Aβ system. AD is envisioned to be caused

sporadically by metal ion dyshomeostasis and oxidative stress enforced by chemical aging or specific life styles that put stress on the APP/Aβ metal transport system. In familial AD, mutations may lower the proficiency of the normal metal transport function of Aβ either by 1) changing the ratio or levels of Aβ to stress the metal homeostasis (Swedish mutation, PSEN1 mutations), or 2) by directly changing the metal-binding capabilities (N-terminal FAD APP mutations), or 3) cross-membrane transport properties of Aβ itself, which depend on the peptides amphiphilic nature; most of the FAD APP mutations increase the hydrophobicity of Aβ which would reduce the release tendency of the peptide from the membrane. This insight is important to move toward a general unified mechanism of sporadic and familial AD as recently attempted from a different perspective[497], a unification of the amyloid and metal ion hypotheses, and an explanation of the normal function of APP and Aβ[498,499]. In the next section, various general strategies to attack these different pathways are summarized.

6.1. Gain of toxic functions: Redox toxicity. The study of metal-induced Aβ toxicity assumes that Aβ gains a toxic function upon binding to metal ions that defines AD. Although Aβ has many interaction modes that could contribute to disease, it is clear that Aβ alone cannot cause AD[64]. The way APP mutants cause AD cannot be coherently described by Aβ properties alone, neither by levels or ratios, aggregation tendencies, or toxicities[61], suggesting that a trigger of Aβ pathogenicity is needed. Some people can handle high amyloid levels[500], indicating that a trigger is needed. Aβ is there all life but AD is only triggered by aging, suggesting that an age-enforced trigger is needed to make Aβ pathogenic (metal dyshomostasis and oxidative stress are aggravated by aging[62]). AD initiates in hippocampus but Aβ is present throughout the brain, suggesting that a trigger is present there (hippocampus is enriched in metal ions, viz. Table 1). So far, all amyloid-alone therapies have failed in clinical trials, suggesting that something that confers pathogenicity to Aβ is missing; the list of arguments continues with the strong evidence that Aβ is in its essence a metal binding peptide[64], and with the role of metal ions in defining the conformations and properties of Aβ discussed above. The

toxic mode of action could take place within the cells or, as many data suggest, within mitochondria that are particularly vulnerable to oxidative stress[150,501,502].

Chemical aging of Aβ as the culprit of AD is a simple mechanism that maintains the importance of Aβ as gaining a toxic function in neurons but also solves the issue of the age-trigger, i.e. that Aβ produces oxidative stress in connection with redox active metal ions, and that this combination causes AD, whereas Aβ by itself is not dangerous. This mechanism is appealing as it maintains support from the data that also support the amyloid hypothesis, including the importance of Aβ-related risk factors PSEN1/2 and APP, but also explains the involvement of metal ions and aging, including oxidative stress in AD brains[503]. The more specific definition of metal ion dyshomeostasis as a shift from protein-bound to free chelatable pools of metal ions[17] renders this mechanism meaningful, both because excess of intra-neuronal free metal ions can exert toxic influences on Aβ molecules, and because simultaneous loss of functional Cu(II/I) and Fe(III/II) from anti-oxidant and energy-producing enzymes such as superoxide dismutase, catalase, and cytochrome c oxidase, would undermine the neuron's ability to cope with oxidative stress; thus redistribution of metal ions is a two-edged sword in AD pathogenesis[17].

While the redox chemistry of Cu(II/I) and Fe(III/II) is toxic to cells in the form of Fenton chemistry[504], Aβ is redox active even without the presence of metal ions. Although Aβ can be oxidized in many ways, the Met-35 is a particularly redox-sensitive residue that is easily oxidized *in vivo* with consequences for Aβ structure and function[505]; in plaques, Met-35 is commonly oxidized to sulfonyl[506]; this type of redox chemistry has been described in detail[27,29][493]. Because Zn(II) is redox-inert, it does not itself take part in redox chemistry. However, by modulation of the electrostatics, notably the induction of electron density towards Zn(II) from the surroundings and the reduced net charge, Zn(II) can elevate the half potential of Aβ, probably making it less prone to redox chemistry *in vivo*; this may explain the protective effect of Zn(II) binding to Aβ [461][491].

It is instructive to consider from general copper proteins the observation that two-electron reduction requires either more than one copper site or a redox-active amino acid ligand, typified by tyrosine, whereas one-electron reaction is feasible upon formation of a Cu(II)-superoxo species[209]. This analogy leaves at least three options for Cu(II)-Aβ based redox chemistry: Cu(II)-Aβ dimer formation and two-electron reduction, potentially involved a bridging peroxide; Cu(I)-Tyr-10 two-electron reduction; and one-electron reduction to yield a Cu(II)-O_2^- intermediate that is reduced by an external reducing agent (or another ligand in Aβ than Tyr-10). Mono-copper enzymes such as amine oxidase provide an example of the latter while the first would correspond to a constituted dicopper enzyme of the tyrosinase type; exploring these analogies further in Cu(II)-Aβ would be of interest.

Indeed, Cu(II) binding to Aβ enables rapid reduction to Cu(I) and production of H_2O_2[459,460], and Cu(I)-Aβ may further react with H_2O_2 to produce harmful hydroxyl radicals[507][508]. A plausible mechanism has been suggested for the H_2O_2 formation that involves first a distinct Cu(II) reduction and then, upon binding of O_2 to Cu(I), a typical Cu(II)-superoxo intermediate which can lead to H_2O_2 upon proton-coupled electron transfer[509]. An important issue is the source of the protons. One appealing option would be that Component I provides a proton to the superoxide, which would facilitate the second reduction to produce HO_2^-, which would then go to solution. Another interesting question is whether beneficial redox activity can also documented for Cu(II)-Aβ or Zn(II)-Aβ, e.g. by reverse superoxide dismutase like reaction, as has been suggested[430]. Fluorescent probes can monitor changes in zinc and copper to potentially diagnose such toxic chemistry[510], and such probes have recently been designed to directly monitor Cu(II)-Aβ induced oxidative stress[511].

The half potential of Cu(II)-Aβ was originally reported at +0.7−0.8 V vs. SHE (converted from Ag/AgCl)[459]. This value is very large: For comparison, the half potential of Cu(II) reduction for $[Cu_2(H_2bim)_2]$ (a typical complex having EPR parameters similar to Component I) is approximately +0.3 V vs. SHE[458], and the standard half potential of relevant mono-copper T1 and T2 sites is

typically in the +0.2−0.4 V range[512][513][514]. The half potential reported for Cu(II)-Aβ_{1-16} at 0.34 V vs. NHE thus seems more reasonable[515]. Another recent estimate is 0.18 V vs. NHE[516], similar to what would be expected.

Depending on the half potential *in vivo*, the Cu(I)-Aβ species may be formed in the presence of even modest amounts of reducing agent. The major reducing agent in neurons, ascorbate, is present in concentrations of 0.01−10 mM[517] and, although usually considered an anti-oxidant, plays a potentially harmful role in Fenton chemistry by enabling the redox cycling to the low-valent metal ion states that can cleave the O−O bond of H_2O_2 to form hydroxyl radicals. In the vicinity of Cu(II)-Aβ, ascorbate can work as a "pro-oxidant" by enabling repeated formation of Cu(I)-Aβ that then produces hydroxyl radicals, analogously to Fenton-type reactions. This dangerous combination of ascorbate and Cu(II)-Aβ was described more than ten years ago[507][518].

As mentioned in section 5.2, during the redox cycle, Cu(II) changes from its coordination number of 4 or 5 to a linear Cu(I) geometry defined by His-13 and His14, implying major structural reorganization in this process[519]. Some NMR studies suggest that, while the first coordination sphere changes substantially to the linear coordination mode of Cu(I), the remaining parts of Aβ is largely unaffected by the reduction to Cu(I)[519]. Aβ misses the advantageous fixed ligands that minimizes the electronic reorganization energy in copper-based electron transfer proteins[209][520,521], and one would expect relatively low electron transfer rates on this basis. Due to the dynamic nature of Cu(II)-Aβ it is possible that some conformations are particularly prone to electron transfer[522], however the need for energy-costly ligand dissociation remains. Thus, even with the Cu(II)/Cu(I) half potential of Aβ in the physiological relevant range, it is not clear if the redox toxicity is physiologically relevant since it depends also on concentration, target engagement, and electron transfer rates. The rate of electron transfer and redox potentials in combination with other relevant electron acceptors and donors under quasi-physiological conditions may therefore be carefully considered in future work.

6.2. Gain of toxic functions: Membrane interactions. It is well-known that Aβ can form pores in membranes and increase permeability of metal ions such as Ca(II)[204,205,330,523]. This ability relates well to the increasing helix propensity of the peptide in low-dielectric and membrane-like environments[3]. Commonly, this feature is associated with the possible toxic mode of action of Aβ in relation to the disease, although this feature cannot be directly related to clinical data; however, what can be shown is that more hydrophobic Aβ variants are more toxic[113,114]. In principle, this may not be due to increased aggregation but could equally well reflect increased membrane pore formation, as both interaction types would be favored by hydrophobic exposure. Indeed, the longer $A\beta_{1-42}$ isoform seems more prone to form membranes, consistent with this point[444], although $A\beta_{1-40}$ has been associated with this tendency in other studies[443]. Yet mainly the self-aggregation in the presence of ThT has been studied in detail in assays relating to disease mechanisms.

In this context, it is notable that ThT response measures fibril formation that is *not* likely to be the relevant morphology of membrane interaction, whereas amorphous, perhaps metal-induced aggregates and oligomers would be relevant. Many still associate a high ThT response with possible toxicity, and aggregation tendency does correlate with toxicity measured in cell assays, but quite plausibly the true correlator is membrane interaction, as they both tend to correlate with hydrophobicity[113]. Recent data suggest that for the model system of increasing pathogenicity A2T < WT < A2V, the most pathogenic A2V is the *least* ThT-responsive variant[382], but an opposite tendency is seen by others[524]; this disagreement clearly needs to be settled. Meta-analysis suggests that ThT responsive (as the common proxy of aggregation) is unrelated or even inversely related to clinical severity of Aβ variants, with the severe but aggregation-resistant Flemish and Osaka variants and the aggregation-prone but mild Tottori variant being notable examples[61]. These findings fit with the view that oligomers, rather than large insoluble fibrils, are involved in the

disease[144,336,351,525]. It is conspicuous that Cu(II) induces such small aggregates that are distinct from and even prevent fibril formation[488,526,527][528].

Given the typical nM concentrations of Aβ within neurons, Aβ molecules will encounter membranes and other molecules much more often than they encounter self-interaction and aggregation. In contrast, at the synapses and under the influence of metal ions, the self-interaction is probably much more favored because both Cu(II) and Zn(II) and Aβ[529,530] are localized in these areas, probably as part of their normal function[169]. The synaptic resting concentrations of copper are ~ 1 μM, but peak levels can reach up to 0.25 mM.[190]. Thus, membrane interactions of Aβ are probably at least as important as self-interaction.

The most established toxic consequence of Aβ membrane interaction is the calcium disruption that results from excessive pore formation by Aβ[173,531,532]. Recently this pore formation has been associated with calcium import into neurons[533][534]. This mode of action could be responsible for the broadly established calcium dyshomeostasis of AD[171,535,536], which has also been linked to PSEN1 phenotypes[174,264], although the latter relationship has been disputed[537].

6.3. Increased neuronal energy expenditure. The energy hypothesis of neurodegeneration holds that neurons are among the most energy-demanding cells in the body and that neurodegenerative diseases are systemic and multifactorial, thus requiring a systemic explanation, energy[538]. Survival times of patients with SOD1-mutation-caused amyotrophic lateral sclerosis (ALS) correlate with the calculated energy cost of maintaining a constant pool of functional SOD1 mutants in wake of their loss of stability and aggregation[538], a theory that is now gaining increasing evidence[539,540][541]. Importantly, protein aggregation represents not just a potential gain of toxic function but also a loss of functional protein. AD patients have been known for many years to have reduced availability of glucose/insulin[542][543], and disruptions in metabolism and energy balance of the brain is an early feature of AD[544]. The energy shortage is a key feature of AD[545][546], and AD is also

characteristically a mitochondrial disease, associated with damaged or otherwise impaired mitochondria, the energy producing organelles of cells[149,502,547].

Energy costs play out in several ways[548], both by the cost of synthesizing new functional proteins to substitute those lost by aggregation, by metal ion imbalances that increase ATP costs of active ion transport and ion gradients in neuronal signaling, and by the increased costs inflicted by degrading and disposing of misfolded and aggregated proteins[549], a cost that seems to have been minimized by evolution[549–551]. All these pathogenic features can be combined into one determining factor, the energy available to each neuron after subtracting maintenance energy costs[3,538]. It would be surprising if all the protein oligomers and aggregates found in various neurological diseases have distinct molecular toxic modes of action. Within the energy hypothesis[538], these protein aggregates are instead common signs of the same thing – exhausted neurons.

In the same way as protein aggregation, a unifying disease mechanism of metal dyshomeostasis has also been missing. During metal dyshomeostasis, loss of functional metal ions will increase the turnover of metalloproteins and at the same time, the free metal ions will interfere with cellular processes such as the ion gradients and ATP-costly metal transport; these two processes (ion gradient maintenance and protein turnover) are the most energy-demanding processes in neurons. Thus, metal-enriched extracellular plaques of AD becomes a sign, not necessarily of toxic metal ions or Aβ overload *per se*, but a sign of neuronal exhaustion and resulting inability to handle basic homeostasis. It is important to distinguish systemic energy loss from the distinct molecular toxic modes of action generally considered because they require different therapeutic strategies. Thus, a broader engagement of both specific *and* systemic (i.e. energy-based) targets may be a promising avenue in future drug development efforts, with new anti-inflammatory and energy-related functions added; for example, in the form compounds that increase glucose uptake[552][553].

6.4. Loss of natural functions: Metal transport. APP-related proteins have normal, beneficial physiological roles in neurons: APP localizes in the pre- and postsynaptic compartments and is expressed in glutamatergic neurons[125][554]. Removal of APP reduces synaptic proliferation, whereas the related amyloid precursor-like protein 2 (APLP2) does not seem to have a large effect on neuron function[555]. Yet, removal of *both* APP and APLP2 is lethal[556][557]. The proteins seem to be involved in maintaining synaptic plasticity[558][559][560] and are important for hippocampus function of mice[561]. Also, AICD regulates transcription in a way similar to that of Notch also produced by γ-secretase[562]. These aspects show the important role of APP and its cleavage products[29].

Aβ is also known to have natural functions in neurons[166–169,499]. Concentrations below nanomolar (as typically relevant within neurons) are neurotrophic whereas micromolar concentrations (as often used in cell assays) tend to be toxic[168][170], although toxic lower concentrations have been reported[137][563]. This raises the major question whether the instantaneously induced toxicity of extremely high Aβ concentrations measured in cell viability assays is relevant at all, considering Paracelsus' principle that the dose makes the poison. As mentioned above, the most toxic Aβ variants are not the most clinically severe[61]. It also raises the question, posed 15 years ago by Smith and al.[499] whether, in the light of Aβ's redox-protective properties, the efforts to strictly reduce Aβ levels is meaningful at all; history has largely proven these considerations right.

Reduction of $A\beta_{40}$ levels by secretase inhibitors or Aβ antibodies is lethal to cultured neurons, and $A\beta_{40}$ is protective in a concentration-dependent way, while the longer isoform, $A\beta_{42}$, did not show beneficial function[564]. Aβ depletion impairs the neuronal function of mice[166]. Aβ monomers protect against copper- and iron-induced toxicity[167] and extracellular Aβ correlates with increased release probability of the synapses[169]. Aβ forms channels that enable calcium transport through membranes[146,204,523,531,565].

Synapses are targeted by Aβ[566] and synaptic structure is affected by Aβ[530]. Short-term synaptic facilitation can be disrupted by both too high and too low levels of Aβ[169]. Synaptic activity requires the repeated flow of glutamate, calcium, and zinc in order to enable neuron signaling and memory formation[17,35,187,531], providing the rationale for such a function of Aβ in synapses. Aβ induces permeability of cell membranes by channel formation[144,204,523,531,565]. Aβ cation-selective channels are inhibited by zinc[329][205][532], suggesting that Aβ is important in maintaining relative levels of Cu(II), Zn(II), and Ca(II). Indeed, zinc exposure increases Aβ production from APP and leads to Aβ deposits[305].

So far, the community has considered metal-interactions with Aβ almost exclusively as a toxic mode of action. Yet, while metal dyshomeostasis is a plausible cause of AD, the studies cited above indicate that *Aβ could itself be a natural metal chelator that protects neurons from such dyshomeostasis* by exporting excess free Cu(II) and possibly other divalent metal ions across neuronal membranes at the synapses with tightly controlled levels regulated by the action of metal-sensitive secretases[3]. If so, it is not surprising that overproduction of this peptide in cell viability assays would lead to toxicity even as it has a normal function, by disturbing this function.

The redox chemistry of Aβ does not have to be pathogenic but could be protective. Indeed, the superoxide dismutase-like Cu(II) binding site of Aβ, which is emphasized by the possibility of a bridging histidine to produce a dinuclear active site in membranes[430], combined with Aβ's ability to localize within mitochondria could indicate a redox-protective role of the peptide. Monomeric $A\beta_{1-40}$ can reduce metal-induced redox toxicity[167]; however whether this occurs by export of these metal ions from the neurons or by explicit redox processes (or both) remains to be determined.

The suggested function of Aβ outlined above was recently supported by studies showing that both zinc and copper regulate the cleavage of C99 (the fragment produced from APP by β-secretase) by γ-secretase by two distinct mechanisms: Zn(II) changes the substrate C99 into degradation-resistant

dimers to prevent cleavage by γ-secretase and thus, Aβ production, in a process that involves histidine residues His-6, His-13, and His-14. In contrast, Cu(II) binds to the subunits presenilin and nicastrin of γ-secretase to inhibit cleavage of C99[567].

7. Perspectives for treatment

7.1. Treatment based on the metal ion hypothesis: Metal chelation. With the rapidly advancing insights into the fundamental role of metal ions in modulating Aβ function, a number of new ideas for therapeutic approaches to AD have been considered[33][69][568]. Several strategies can be separated: One is to target metal dyshomeostasis *per se*, without any concern for Aβ; another is to target the perceived toxic metal-Aβ species either by preventing their association or their combined function; a third is to address the downstream toxicity caused, notably by the use of anti-oxidant or anti-inflammatory molecules[29,569]. Some strategies involve a combination of several of these targets, and some molecules, such as curcumin-derivatives[570,571], cover many of these functions in one molecule.

Starting with the first strategy, dedicated metal ion chelators with a desired specificity for Cu(II) and Zn(II) can be designed to reconstitute normal Cu(II) and Zn(II) levels within the neuron, assuming that these levels are subject to pathogenic imbalances[572–574]. The relevant focal point for this activity is probably the synapses where Cu(II) plays a role in transmission, or in the mitochondria where neuronal energy is produced. A variety of metal chelators reduce amyloid plaque formation[575], and they also work to down-regulate APP expression and lower Aβ levels[576]. Strong metal chelators such as EDTA reduce γ-secretase activity and thus Aβ production[577].

For these approaches, one needs to consider the relevant *affinity* of the drug towards each metal ion but also their relative affinities (i.e. the *specificity*), because the relative levels of the metal ions are

important due to their interactions[17,191,230]. One also needs to define a desired concentration range and affinity range: In a recent definition, metal dyshomeostasis in AD takes the form of a shift from bound metal ions in proteins (typical K_d < ~10^{-7} M) to loosely bound, chelatable metal ions (typical K_d > ~10^{-6} M)[17]. This working definition provides a desired range of K_d, which however needs to be modified by the physiological concentrations of competing ligands and metal ions.

The first AD drug candidates of this type were clioquinol derivatives[573][578]; the working mode is evident from their effect on copper levels *in vivo*[579]. These compounds are well-known metal chelators with good metal-binding affinities but also with known historic side effects that reflect the narrow K_d window *in vivo*[580]. Derivatives of clioquinol can be tailored for higher affinity to remedy Cu(II)-induced toxicity, interestingly at the same time reducing Aβ aggregation[581]. Beneficial effects of metal chelators on Aβ status in cultured cells[582][583] and in *Drosophila* that expresses human Aβ[584], and on the cognition of mice[574] support this strategy.

This treatment mode in principle targets general metal ions in the tissue where it is applied. However, in the special circumstance that Cu(II)-Aβ represents the most labile pools of copper, and the chelator has a K_d for Cu(II) < 10^{-10} M, Cu(II)-Aβ species would be stripped of their copper if the concentrations of Aβ and drug were similar and other competing ligands could be ruled out, as is commonly the case *in vitro*, but rarely *in vivo*. If the chelator binds more weakly, it will mainly target free, chelatable Cu(II) with K_d > 10^{-9} M, dependent on the concentrations of the drug, Aβ, and competing ligands available to chelate the free Cu(II) pool. A concern is that the *in vivo* concentration of free competing ligands is orders of magnitude larger so that even a potent chelator will need high concentrations to compete for Cu(II) *in vivo*. Also, the drug needs to be active where the surplus of metal ions occurs, and it needs to retain the metal ion and export it from the brain or at least from the immediate environment of the vulnerable neurons. Finally, it should not bind excessively to functional metal ions.

Future objectives in this direction will be to provide Cu/Zn selective chelators that rebalance the intra-neuronal Cu/Zn ratio, which seems to play a role in the disease[3], and to elucidate the distinct target pools of Cu(II) and Zn(II). In the synapses where Aβ may actively transport Cu(II) and Zn(II), Aβ will be an important competing ligand for the chelating drug, and potentially, the role of the drug will be to aid copper export under these conditions. With Zn(II) and Cu(II) concentrations in excess of 10−100 μM during peaks of activity in these areas[585] and Aβ being probably concentrated in these parts at much higher than the nM levels found globally, the chelator drug needs to directed specifically to the synaptic clefts and possibly into the neurons in the relevant parts of the brain, which is a formidable task.

7.2. Metal-Aβ targeting compounds. A second strategy is to target the direct interaction between metal ions and Aβ, to change the properties of the complexes. Clioquinol is a direct chelator but also interacts with metal-Aβ complexes, providing an example of a metal-protein attenuating compound[578]. The separation of metal-chelation and direct targeting of Aβ is not always completely clear[586]: In the first case, the ligand competes for the free metal ions to lower the *concentration* of metal-Aβ complexes, whereas in the second case, it binds metal ions and Aβ directly as a ternary complex to modify the *behavior* of the metal-Aβ complexes. Notable work towards distinguishing metal-Aβ and metal-free Aβ targeting has recently been reported that builds on the monitoring of distinct ternary complexes[587]; this mechanistic distinction will be very important to future drugs development efforts.

Small molecules that can probe and interact with metal-Aβ complexes are increasingly sought by a variety of strategies[588][589]. These include synthetic flavonoids[590] and the use of small peptides that can be tailored to recognize and interact with Aβ and inhibit fibrillation and neurotoxicity[591][592].

7.3. Anti-oxidant and anti-inflammatory molecules. It has been known for decades that oxidative stress is a central and one of the earliest histopathological features of AD[28,29,593][594], and the most logical age trigger of the disease[29,595]. Although the beneficial role of antioxidants on AD[596] has been debated[597], the data at hand strongly implies that anti-oxidants should be considered as part of any AD therapy. Incidentally some of seminal early work in this direction also showed that Aβ deposits may be protective features against oxidative insults[461][594]. Many anti-oxidant molecules pursued as AD treatment are natural multifunctional compounds as discussed in section 7.6, whereas some are natural, but not multi-functional, e.g. ascorbate and α-tocopherol[598].

Inflammation is also a recurrent feature of AD, although its causal role is debated[599][600,601]. Yet regardless of its place in the disease etiology, it would probably be beneficial to reduce inflammatory responses as part of a wider treatment strategy[602]. These strategies generally divide into steroid hormone-based and non-steroid anti-inflammatory drugs (NSAID)[602], which have shown particularly beneficial effects in clinical tests, and most (but not all) meta analyses confirm this effect[603][604][605][606][607]. It has been of major interest that NSAIDs such as Sulindac and ibuprofen reduce the levels of longer Aβ forms (notably $A\beta_{1-42}$), with corresponding increase in shorter isoforms[608]; this remarkable effect has been the basis of attempts to develop γ-secretase modulators that specifically alter the long-short ratio of Aβ[122]. It is not clear that target engagement is the main mechanism of NSAIDs but it does imply a very interesting relationship between APP processing and inflammation.

Within the metal ion hypothesis, the performance of NSAIDs could be explained by the general fact that zinc homeostasis plays a central role in inflammation, and zinc administration by itself is anti-inflammatory[609][610–612]. NSAIDs are known to increase zinc levels in the brain[613][614], which in turn are known to regulate cleavage of APP-related proteins[273,615]. Increased zinc levels have recently been found to increase the long-short ratio[567], as seen with NSAIDs. Thus, the assumption

that NSAIDs engage γ-secretase is not required to bring about this effect of NSAIDs: If NSAIDs work, they probably do not modulate γ-secretase-activity by target engagement but by the pathways outlined above.

Since Cu(II) and Zn(II) homeostasis is tightly regulated and antagonistic[230][229][616], any strategy that targets Cu(II) selectively may increase anti-inflammatory Zn(II) levels. However, anti-inflammatory and anti-oxidant molecules may be developed for targeting neurons without any direct appreciation of this role of the metal ions, and, by the relationship to Cu(II) and Zn(II) in these pathways, may still have an influence on these levels, or, they do have a direct influence on these levels by themselves.

7.4. Treatment based on multifunctional molecules. Given the complexity and multi-factor nature of AD, the use of multifunctional molecules is likely to become a main treatment paradigm[177][617]. Among these, compounds can include several functions into one: 1) target the specific metal-Aβ interactions to modify this interactions; 2) chelate metal ions alone to balance metal ion levels, 3) target Aβ alone in (in principle) any of its conformational and multimer states; 4) target the toxic chemistry of the processes either separately or in combination, notably by anti-oxidant functions[152][177][588]; 5) target the production of Aβ by β- and γ-secretases[618]; or 6) target additionally signaling pathways such as tacrine-derived molecules[619]. Such multifunctional molecules can be expanded to be increasingly efficient[152,620], and the structure-function relationships defining these interactions are being increasingly studied, as reviewed recently[70][590][621].

The rational combination of features from several molecules is a very useful strategy, as shown in the development of multifunctional antioxidants against AD[622], or phthalimide and saccharide derivatives that both target Aβ production and aggregation[618]. There are recent attempts to rationally combine most of the features defined above[623], which is attractive in terms of the chemical

creativeness that it illustrates, but more importantly, it is perhaps a necessary approach to treating a complex multifactorial disease such as AD. Molecules that contain both metal chelation and anti-oxidant properties can also be devised, including e.g. systems that use cerium oxide together with metal chelation function to reduce aggregation and provide anti-oxidant conditions at the same time[624].

7.5. Metal-based Aβ degrading compounds. Originally, enhanced clearance of Aβ pools were seen for clioquinol and interpreted as indicating an Cu(II)-dependent upregulation of matrix metalloproteases that can degrade Aβ[625], a result that has been reproduced[626]. Similar effects have been seen for the clioquinol derivative PBT2[627]. Since most of the natural peptidases that degrade Aβ are zinc peptidases[287,628,629], zinc peptidase mimics and other metal complexes capable of hydrolyzing Aβ are interesting compounds to pursue[630].

A promising new approach is to use stereospecific metal complexes to hydrolyze Aβ peptides. Recently, tetra-*N*-methylated cyclams have been found to cleave Aβ peptides and counteract aggregation[631]; this may provide an alternative way to restore amyloid balance in neurons if such systems can be implemented as drugs.

7.6. Multifunctional natural compounds against AD. It is notable that many promising AD drug candidates are natural compounds, implying that not only medicinal inorganic chemistry but also natural compound chemistry is currently thriving within the AD area. Only a few examples will be mentioned as this area has been reviewed extensively[17,568,570,632–634].

Polyphenols such as epigallocatechin gallate (EGCG) found in green tea have been particularly in focus[635][636][637]. In addition to their antioxidant functions[636,638], polyphenols can substantially reduce Aβ aggregation either by direct interaction with Aβ or by interaction with metal ions, or as ternary complexes[639][636]. In addition, phenylpropanoids from cinnamon[640] and coffee[641] have β-secretase regulating and anti-aggregation functions. Curcumin derivatives are widely explored as drugs[570,642,643] against AD and work as anti-oxidant metal chelators and

interact with Aβ[491,570]. The natural role of such compounds in modulating Aβ-metal relationships is intriguing considering e.g. how such compounds may reduce risk of AD[17,570,644–646].

Ginkgo has long been associated with as possible beneficial role in AD[647–649]. Bilobalide and related compounds from ginkgo may reduce Aβ production by inhibiting β-secretase activity[650], and treatment has been shown to improve transgenic AD mice[651]. Also, various flavonoids[590][652] and alkaloids such as berberine[653,654] have shown β-secretase inhibiting effects. Flavonoids such as luteolin has been reported to counteract Cu(II)-induced toxicity and reduce ROS generation[652].

Metallothioneins are small cysteine-rich metal-binding peptides that bind 4+3 divalent metal ions, typically Zn(II), in two subunits, but can also bind Cu(I) with higher stoichiometry; they fulfil many of the desirable properties discussed above[655] and have been called "multipurpose proteins"[656]. Functions include buffering of metal levels, direct exchange of metal ions with Aβ, and antioxidant properties[17,655–657]. Notably, MT-3 can exchange metal ions with Aβ[658], and this may be a way to prevent Cu-Aβ toxicity[659][660]. Metallothionein levels are already increased in AD patients[17,251] and in aging human brains[62]. Metallothioneins achieve their selectivity and buffering role through evolution of two distinct sites with different affinities for metal ions, caused by the increased negative charge density in the smaller β-site compared to the larger α-site[661,662]; this may perhaps serve as inspiration for multifunctional molecules also having multiple metal binding sites. Thus, metallothionein mimics have also been suggested as promising multifunctional drugs for treatment of AD[17,572].

7.7. Strategies aiming at balancing Aβ normal function. The beneficial effect of monomeric Aβ in protecting against metal-induced redox toxicity resembles the effect of classical metal chelators such as EDTA[167]. Inhibition or depletion of $A\beta_{40}$ by secretase inhibitors or Aβ antibodies kills neurons[564], and Aβ depletion impairs neuronal activity in mice[166]. Considering the worsening

effects of many Aβ reducing drug candidates, new drug strategies should attempt to preserve or reconstitute functional monomers rather than strictly reduce Aβ levels, i.e. distinguish between beneficial and harmful forms of Aβ[3]. The neuronal production of beneficial Aβ should be protected, and possibly enforced, while harmful Aβ species should be targeted by stripping them of redox active metal ions, dissolving them, and export them from the neurons.

As argued above, the normal function of Aβ may be to balance intra-neuronal Cu/Zn levels during e.g. synaptic activity in copper- and zinc rich neurons of the hippocampus where AD sets in early. Considering the normal roles of Aβ, balancing of Aβ may be as important as respecting a therapeutic window of metal ions in chelation therapy, considering Aβ's known therapeutic window[461][170]. For example, antibodies that selectively bind harmful amyloid species but do not interfere with beneficial metal-binding functions of monomer Aβ would be of interest[15], as would protection of beneficial interactions of Aβ with other cell ingredients[663]. Another emerging natural role of Aβ is in immune defense[664][665], which partly relates to the inflammatory pathways briefly discussed in this review. In combination with molecules that target the energy crisis and mitochondrial disease of AD[161,666–669] and distinct metal regulatory pathways[670], there are many promising directions to future therapies in AD that should replace the amyloid-alone strategies as a main priority in efforts to tackle this dreadful disease.

8. Conclusions

In this paper, both the structural chemistry and coordination chemistry of Aβ have been reviewed in relation to the commonly assumed toxic functions but also to beneficial functions in the brain. The review has summarized most of the features that the author considers central to the disease, without going into detail on specific topics, which have been excellently reviewed by others; references to the literature are given in those instances. Starting from the amyloid hypothesis, it is argued how metal binding may be the missing age-enforced event that makes Aβ relevant to the disease and should be considered in future drug development efforts.

Due to the structural variability of Aβ and its many faces, there are substantial challenges associated with studying Aβ and specifically its interaction with metal ions. These primarily relate to the difficulty of preparing monomer samples and producing reproducible aggregation, but also to the methods applied, with ThT assays having issues. Because the morphologies of Aβ are diverse and ThT responsive selective, this assay should be combined with other measures of aggregation behavior. A high ThT response indicates mainly fibrillar β-sheet aggregates that have been associated with less severe forms of Aβ[382], whereas pathogenically relevant oligomers or amorphous aggregates[12,143] may be invisible to ThT.

Most functional studies of Aβ are performed in buffered solutions that do not resemble a molecular crowded cellular environment. The structural ensemble of Aβ that defines its aggregation behavior is very environment-dependent, with helix favored in low-dielectric environments typically encountered in neurons, and with coil favored in water. Thus, aqueous buffered solutions are probably biased towards fibrillation and should be augmented with studies that mimic an intracellular environment e.g. by use of co-solvents or micelles. Consistent with this, fibrils are encountered in the extracellular environment, whereas the amorphous oligomers are the relevant species inside neurons.

As argued in this review, future work should consider also the established beneficial functions of Aβ[206,499]. The amphiphilic properties, helix formation, metal binding and known channel properties of Aβ points towards the natural function of the peptide. The metal binding modes and specific structures enforced by metal ions are often nonfibrillar, and metal ions can both inhibit and accelerate fibril formation. Metal-Aβ structures are pathogenically relevant, both as possible pathogenic species but also as species that transport metal ions across the neuronal membranes, and this transport may be involved in the disease.

The conformational transition to fibril structure is most likely a protective measure to deposit excess metal ions upon age-enforced metal ion dyshomeostasis and oxidative stress. The natural roles of Aβ should be accounted for when defining new treatment strategies, and the review has made an attempt to balance between the needs to target pathogenic forms metal-Aβ interactions and to retain the normal function of Aβ in this process; this balance between loss of gain of function poses new challenges to the emerging use of multifunctional molecules for treatment of AD.

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